



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 48

Alan R. Katritzky

Advances in

Heterocyclic Chemistry

Volume 48

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Advances in

HETEROCYCLIC CHEMISTRY

Edited by

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Preface

Volume 48 of *Advances in Heterocyclic Chemistry* consists of five chapters that break considerable new ground for the series. Oae and Furukawa have contributed what is essentially a double chapter dealing with two important and fast-developing aspects of sulfur heterocyclic chemistry. The first is ligand coupling and exchange in sulfuranes and the second is ipso-substitution in *S*-substituted heterocycles. Cirrincione, Almerico, Aiello, and Dattolo cover diazoazoles. This complements a chapter by Tedder that appeared in Volume 1 of the series but which is now very much outdated. The subject has expanded greatly, and the Palermo authors have much fascinating chemistry to recount.

The elegant cobalt-catalyzed syntheses of pyridines, on which so much work has been done at Muelheim, is aptly summarized by Bönemann and Brijoux. Elnagdi, Elmoghayer, and Sadek complete in this volume a survey of heterocycles containing condensed pyrazole ring systems. Thus, following earlier chapters that have appeared on pyrazolopyridines (Volume 36) and on pyrazolopyrimidines (Volume 41), we now have a complete survey of systems in which a pyrazole ring is condensed with another five- or six-membered heteroaromatic ring.

Last but not least, the thianthrenes, derived from a ring system that is rapidly increasing in importance because of its electronic properties, are reviewed by Joule. Readers are reminded that this volume will contain no index. The last index volume was Volume 46, and we now plan to designate every fifth volume an index volume; thus the next will be Volume 51.

ALAN R. KATRITZKY

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Heteroaromatic Sulfoxides and Sulfones: Ligand Exchange and Coupling in Sulfuranes and Ipso-Substitutions

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I. Introduction

The sulfur atom is well known for its ability to form stable multicoordinated states involving not only di-, but also tri-, tetra-, penta-, and even hexacoordinated compounds. The central sulfur atom in organic molecules can expand its valence shell beyond the normal octet valence to that

of decet or even dodecet. This property is in marked contrast to that of the oxygen atom, although both belong to the same family. Therefore, many types of organic sulfur compounds can be prepared, which are inconceivable for the corresponding oxygen analogues. Hence, organic sulfur compounds have been and will continue to be used widely for modern organic syntheses (62MI1; 68MI1; 77MI1) since organosulfur compounds are quite reactive and undergo numerous novel reactions upon treatment with electrophiles, nucleophiles, free radicals, and oxidizing or reducing agents.

Mechanistic studies of these reactions started in the mid-1950s. The first monograph describing this kind of work was written by us in 1962. The characteristic properties of organosulfur compounds compared to those of oxygen analogues, can be summarized as follows: (1) The sulfur atom can usually be converted to various oxidation states. (2) The sulfur atom can be readily introduced into molecules. It can also be removed easily by treating the molecule with common reagents since the energies of sulfur atom bonds are lower than those of the oxygen atom. (3) The dicoordinated sulfur atom placed at an α -position can stabilize carbanions, carbonium cations, and carbon free-radicals. Tri-, and tetracoordinated sulfur atoms also stabilize carbanions generated at the α -position. Thus, by using these carbanions or carbonium cations stabilized by the sulfur atom, many elegant organic synthetic procedures have been developed. (4) Tricoordinated sulfur compounds can be attacked by a number of nucleophiles to initially form the pentacoordinated sulfuranes as unstable intermediates, which themselves are quite useful. (5) Tri- and tetracoordinated sulfur atoms are intrinsically chiral centers which are quite important in promoting mechanistic investigations and syntheses of optically active molecules (61MI1; 66MI1; 70MI1; 71MI1; 74MI1; 76MI1; 77MI2; 77MI3; 79MI1; 81MI1; 82MI1; 84MI1; 84MI2; 85MI1; 85PS1; 87MI1). Meanwhile, numerous heteroaromatic compounds bearing sulfur atoms have been synthesized and their physical and chemical properties studied. Their chemical behavior has been found to differ depending on the number and nature of the hetero atoms in the heteroaromatics, as well as on ring size.

Physicochemical behavior of these heteroaromatic systems has also been compared to those of the corresponding aromatic systems. One remarkable feature is that the heteroaromatics bearing a sulfur atom are more reactive than the corresponding aromatic derivatives mainly due to the strong electron-releasing or withdrawing property of the heteroaromatics. The latter property is due to the somewhat reduced delocalization of orbitals by the introduction of hetero atoms into the rings (63MI1; 76MI2; 84MI3, 84MI4).

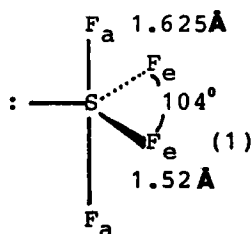
When sulfur functional groups and heteroaromatics are combined, an entirely new field of chemistry emerges. Pharmacological uses have expanded; for example, introduction of a sulfur atom into nitrogen hetero-

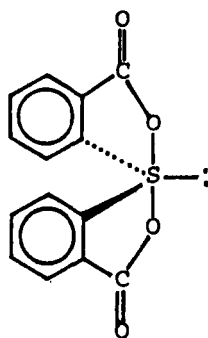
cycles usually increases the biochemical activity many-fold. Thus, numerous heterocycles bearing sulfur atoms or sulfur functional groups have been prepared and used for various purposes such as drugs, agrochemicals, dyestuffs, cosmetics, optical materials, and industrially important starting intermediates. However, no systematic investigation has been carried out on the chemical behavior of these organosulfur derivatives. We have started to explore the chemistry of these azaheteroaromatic organosulfur compounds and have found interesting new reactions. This review only touches on what we believe to be the important chemical behaviors of organosulfur compounds of azaheteroaromatics, particularly pyridine and its related six-membered derivatives. The contents are divided into the following items: (1) a new concept of ligand-coupling reactions and ligand exchange within σ -sulfuranes formed in the reactions of the sulfoxides, bearing azaheteroaromatics, with Grignard and organolithium reagents; (2) ipso substitution and desulfurization reactions of the sulfoxides and sulfones in which both the sulfinyl and the sulfonyl groups become good leaving groups; (3) thione-thiol tautomerism and its applications to the organic synthesis; and (4) miscellaneous reactions on the organosulfur compounds bearing azaheterocycles.

II. Ligand Coupling and Ligand Exchange in σ -Sulfuranes

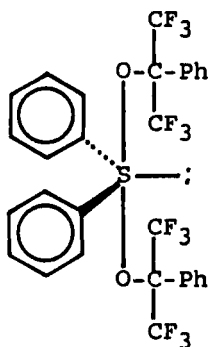
A. LIGAND COUPLING IN σ -SULFURANE INTERMEDIATES

Pentacoordinated phosphorus and sulfur compounds were presumed earlier to be of $3sp^3d$ hybridization (39MI1), however, a three-centered, four-electron bond, called a hypervalent bond by Musher [69AG(E)54], was suggested in the early 1950s by Rundle and others (51JA4321; 85MI2) to be consistent with p -orbitals. The structure of one such compound, SF_4 , is shown (1). Although the original theoretical treatment of hypervalent structures has been modified slightly by the introduction of $3d$ -orbitals into the calculation (74TCA227; 76JA1647; 89PC1). The structural feature of such hypervalent compounds has remained the same.



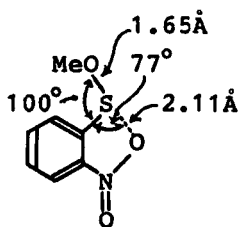


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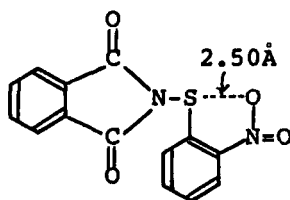


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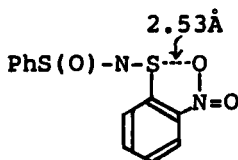
The first examples of stable sulfuranes, one (2) by Kapovits and Kalman (71CC649) and another (3) by Martin and Arhart (71JA2339), were shown to have two polar bonds and longer S—O bonds at nearly 180° . Hypervalent interaction was noticed in the extremely short distance between the neutral divalent sulfenyl sulfur atom and the weakly nucleophilic oxygen atom of a nitro group or a carbonyl group in compounds 4–7 (64JA2339; 82PC1; 86AX(C)121, 86AX(C)124), which were prepared for X-ray crystallographic analyses. Thus, hypervalent bonding is considered



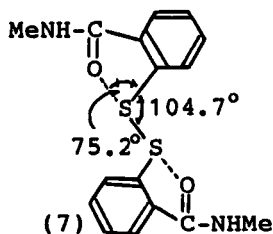
(4)



(5)



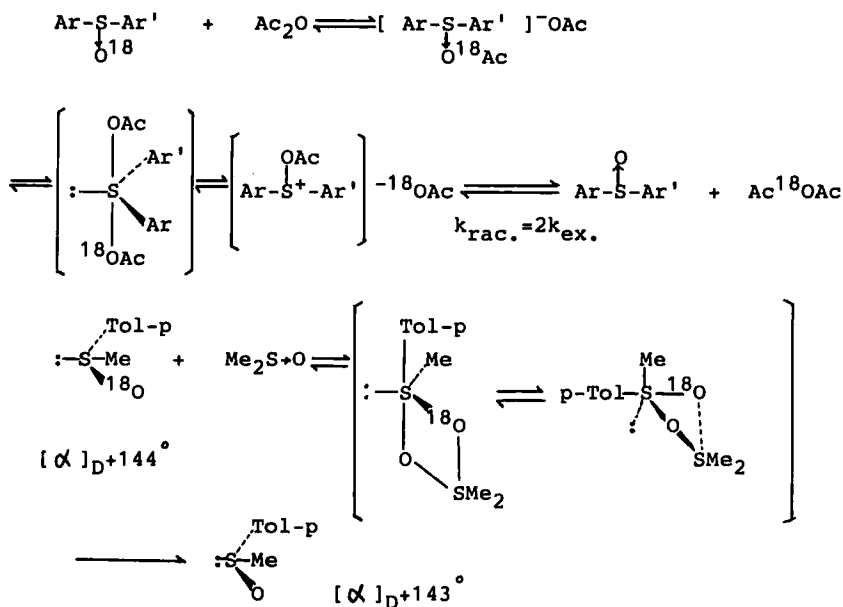
(6)



(7)

to be quite common and readily formed. Another important phenomenon observed in the hypervalent species is the facile occurrence of topological transformation known as pseudo- or turnstile rotation. The most essential feature of a hypervalent species is that the central atom is valence-shell expanded, e.g., the sulfur atom in the σ -sulfurane assumes a decet. Therefore, hypervalent species are relatively unstable, and the central atom tends to resume the normal valency by extruding a ligand bearing a pair of electrons or a pair of ligands coupled with a pair of electrons, affording stable compounds in which the central atom can resume the stabler normal octet.

There are three conceivable ways for hypervalent species to be transformed to stable compounds in which the central valence-shell expanded atom can resume the normal valency by extruding a pair of electrons. One way is by self-decomposition, the best-known example of which is the Wittig reaction [for the historical background, see Wittig (64MII)]. The main driving force of the Wittig reaction is definitely the formation of the high-energy $P=O$ bond, ca~536–578 kJ/mol. The second way is by ligand exchange, the most studied reaction for hypervalent species, which may proceed with inversion of configuration as in an S_N2 process, which is illustrated (Scheme 1) by the oxygen-exchange reaction of sulfoxides (67TL1409). The ligand exchange may also proceed with retention of

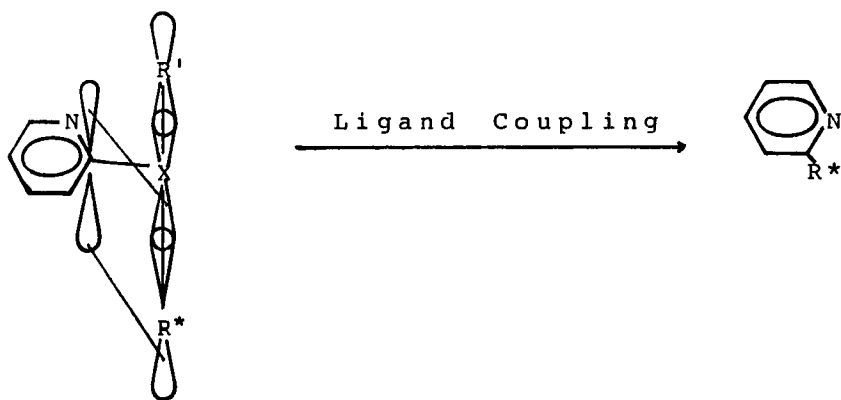


SCHEME 1. Oxygen exchange reaction of sulfoxide.

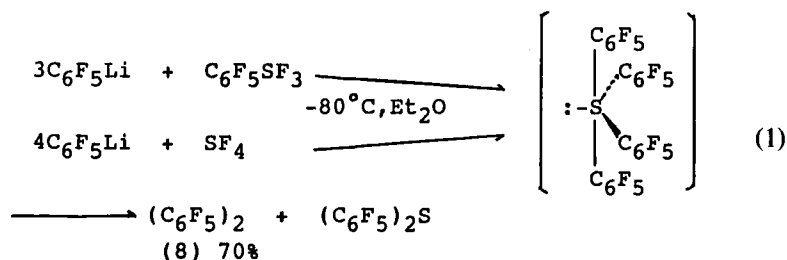
configuration via initial pseudorotation (68TL4131). The phenomenon of pseudorotation is not well understood but seems to be very sensitive to the stereoelectronic charge around the central valence-shell expanded atom (85TL5699, 85TL5703; 88TL4445).

Ligand coupling is the last and least known reaction of hypervalent species. In hypervalent species, axial coordinates are thought to be occupied by electronegative ligands using p-orbitals, while equatorial coordinates, which are of sp^2 hybridized orbitals, are presumed to be taken up usually by π -ligands or electron-donating ligands. Ligand coupling is thought to take place between an equatorial and an axial ligand as illustrated in Scheme 2, which shows ligand coupling of 2-pyridyl at an equatorial axis and an R group at an axial coordinate. If there is any cohesive interaction between the two ligands, they are extruded from the central valence-shell expanded atom, concertedly affording a ligand coupling product in which both ligands hold the original configuration completely. In most cases, the cohesive interaction results from an overlapping of orbitals of both ligands as shown in Scheme 2.

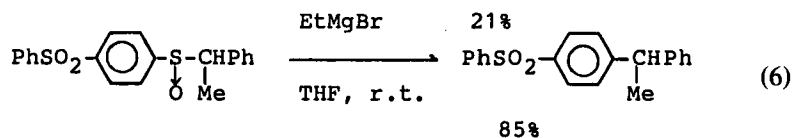
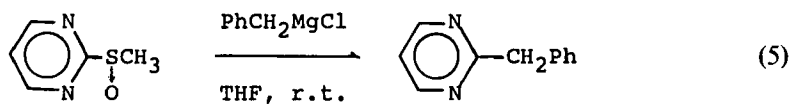
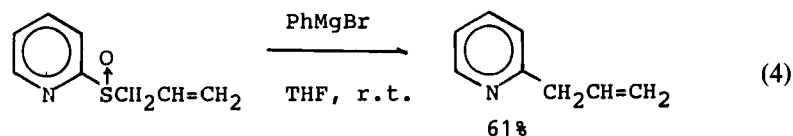
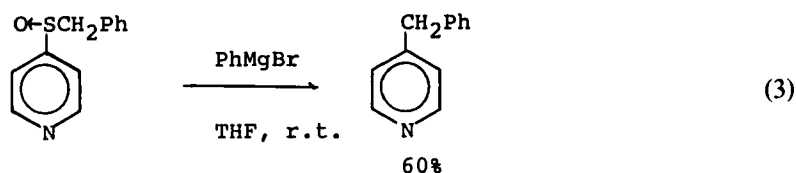
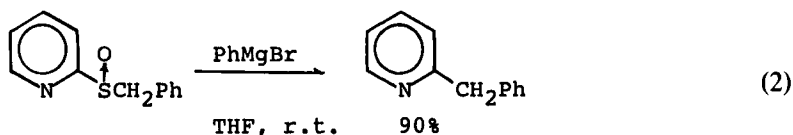
Earlier examples of ligand-coupling were the reactions of triarylsulfonium salts with aryllithium reagents. (69BCJ1968; 69JA2175; 70TL2485; 71JA5597, 71JA6077; 72BCJ2019; 72CC1079; 73JA5288) In one case, Sheppard observed the NMR spectrum of what seemed to be the incipient intermediate sulfurane, which upon warming, gave coupling product **8** (71JA5597) [Reaction (1)]. We have found many examples of ligand-coupling reactions within σ -sulfurane intermediates formed by treatment of both heteroaryl and aryl sulfoxides with Grignard reagents [84TL69, 84TL2549; 86MI1, 86PS13; 87JCS(P2)405, 87PS123, 87PS139; 88H(ip)1, 88MI1, 88TL(ip)1, 88TL(ip)2]. [See Reactions (2)–(6)]. Not only benzyl,

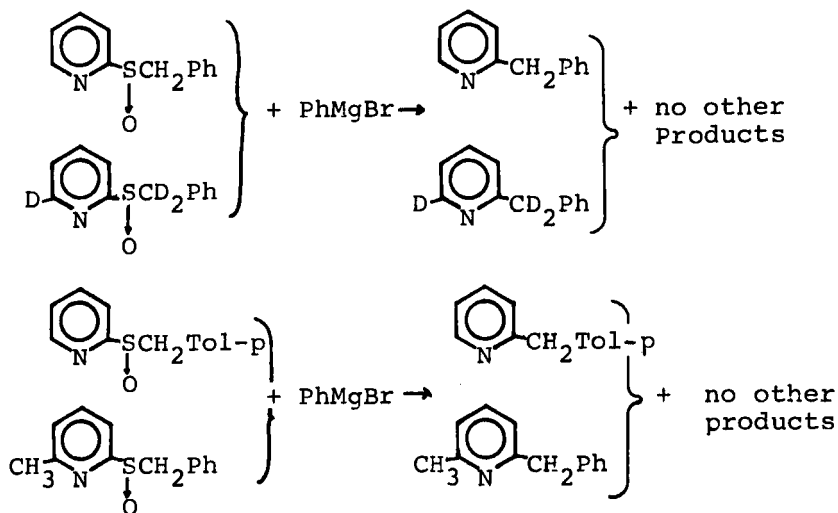


SCHEME 2



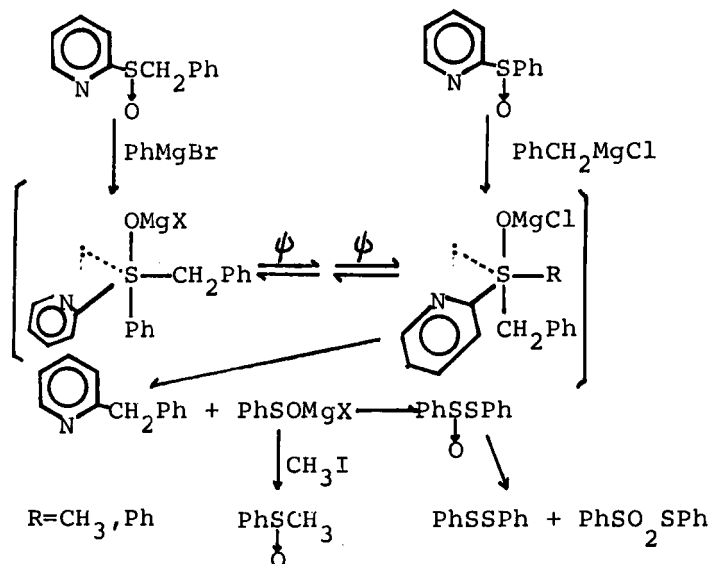
but also allylic, *sec*- and *tert*-alkyl groups can couple with a pyridyl group, while an aromatic ligand bearing an electron-withdrawing group such as *p*-phenylsulfonyl also can replace a heteroaryl group in order to achieve a smooth coupling. The following cross-over experiments revealed the intramolecular nature of the coupling reaction (Scheme 3). The ligand-coupling





SCHEME 3 Cross-over reactions.

reaction to form 2-benzylpyridine is shown in Scheme 4 [85TH1; 87JCS(P2)405, 87PS123, 87PS139; 88H(ip)1, 88TL(ip)1; 88TL(ip)2] The remaining organic sulfur species is PhSOMgX , which can be converted, using methyl iodide, to methyl phenyl sulfoxides or can be quenched with

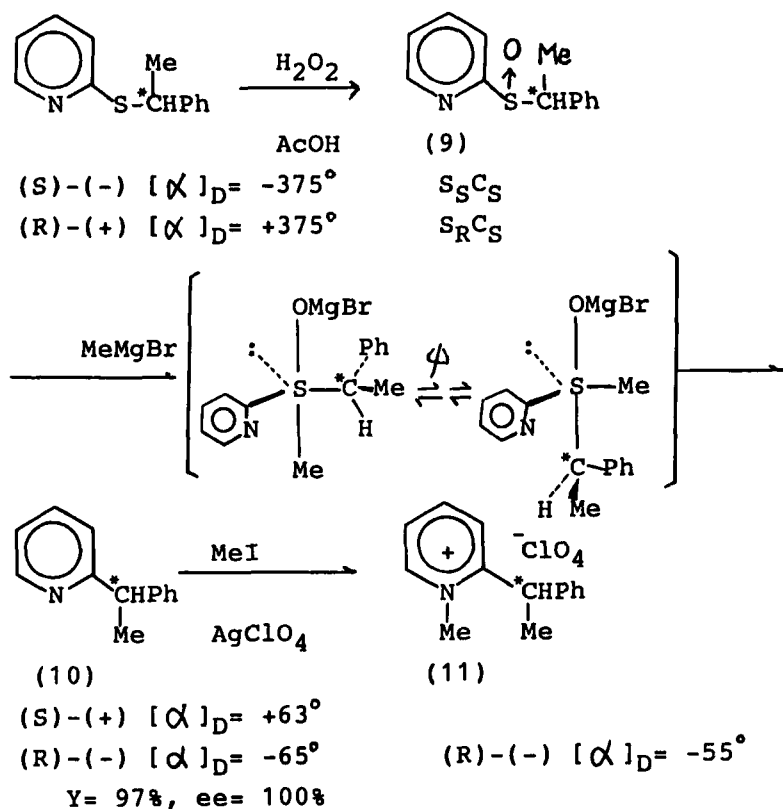


SCHEME 4. Mechanism of ligand coupling.

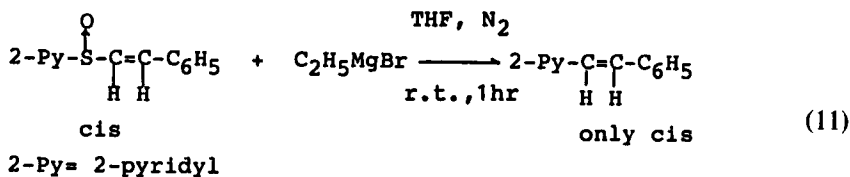
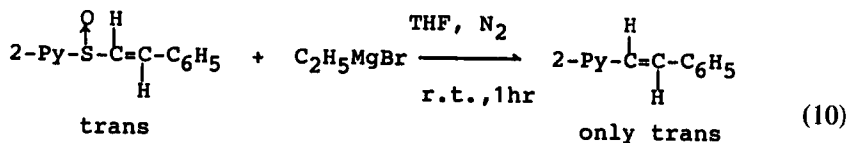
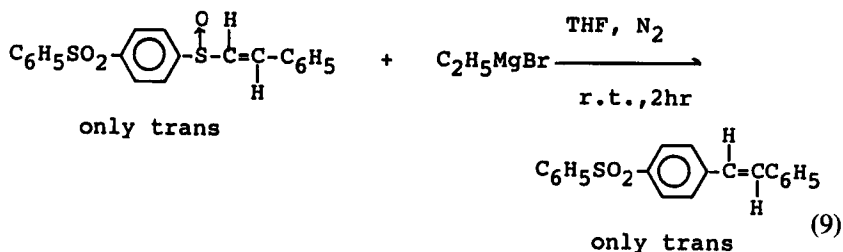
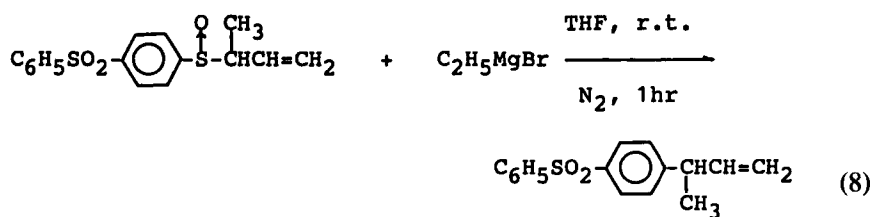
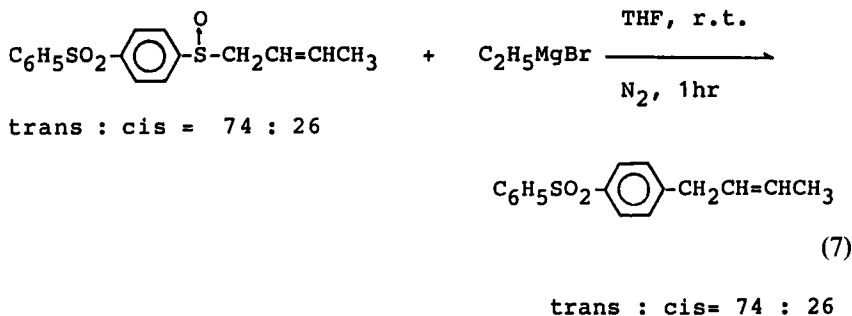
water to give diphenyl thiosulfinate and its disproportionation products (Scheme 4).

B. STEREOCHEMISTRY OF LIGAND COUPLING ON THE SULFUR ATOM

Since ligand coupling was found to proceed nearly quantitatively, a stereochemical study of the coupling reaction was carried out using optically active 1-phenylethyl-2-pyridyl sulfoxide (9) (Scheme 5). When the (S) isomer (10) was converted to crystalline *N*-methylpyridinium perchlorate (11) for X-ray crystallographic analysis, the compound was found to have retained its configuration completely (87PS123). Other examples are shown in reactions (7)–(11). These stereochemical studies, together with



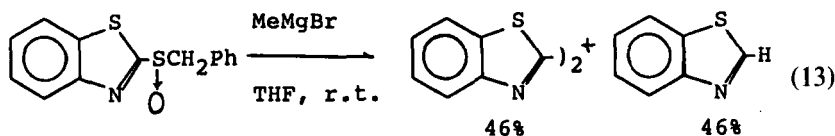
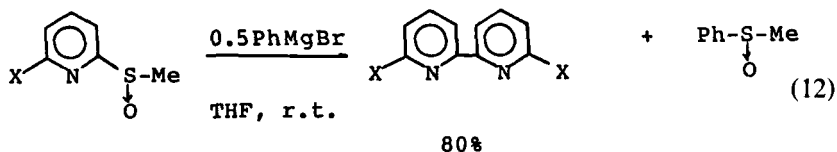
SCHEME 5. Stereochemistry of ligand coupling.

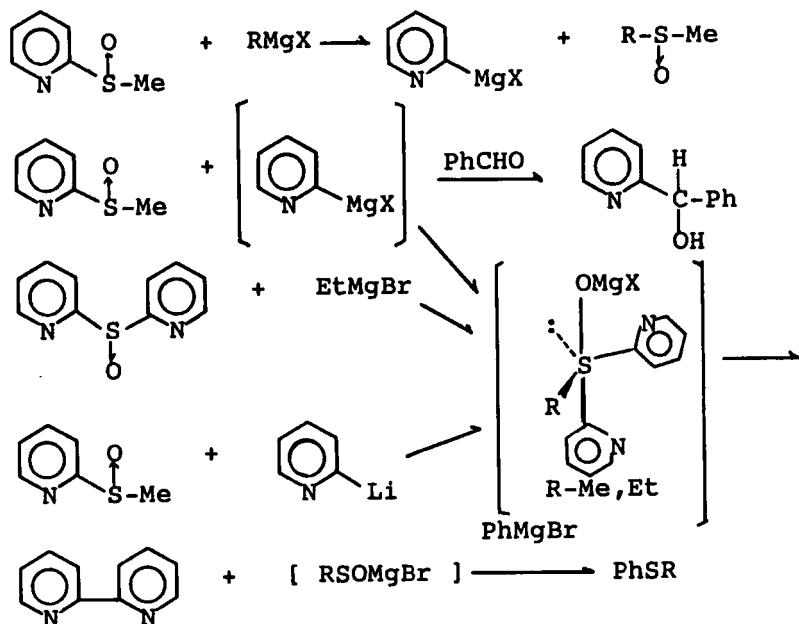


other accumulated observations, clearly indicate that ligand coupling in the σ -sulfurane is a concerted process. If ligand coupling proceeds concertedly, then exactly the same retention of configuration is expected, even with other sp^3 -centered ligands such as allylic groups, which undergo very facile isomerization or rearrangement. However, as shown in reactions (7)–(11), neither the crotyl nor 1-methylallyl group have been found to have changed their configurations at all. In the former reaction, the *cis* and *trans* ratio of crotyl groups has been retained in the same ratio in the resulting ligand-coupling product, i.e., 1-(*p*-benzenesulfonylphenyl)-2-butene [88H(ip)1; 88TL(ip)1, 88TL(ip)2]. In the preparation of 1-(*p*-benzenesulfonylphenyl)-2-phenylvinyl sulfoxide, only the *trans* form was successfully isolated. Meanwhile, both the *trans* and *cis* isomers have been obtained for 2-pyridyl 2-phenylvinyl sulfoxide. Then, both of these isomers were subjected to the usual Grignard reaction [Reactions (9)–(11)].

C. LIGAND COUPLING AND EXCHANGE ON THE SULFUR ATOM

In contrast to the previous examples of ligand-coupling reactions of pyridyl or other heteroaryl sulfoxides with Grignard reagents, if Grignard reagents are treated with sulfoxides bearing different combinations of the ligands other than benzyl and pyridyl, then ligand-coupling and ligand-exchange reactions are observed either concurrently or independently only. In Scheme 6, the initial step is ligand exchange and the subsequent step involves ligand coupling of two identical heteroaromatic groups (87PS123). This was verified by trapping 2-pyridylmagnesium bromide with benzaldehyde; 2-pyridyl phenyl carbinol was obtained in 15 percent yield along with 2,2'-bipyridyl, which was the coupling product. Similar reactions, summarized in reactions (12) and (13) were also found to proceed smoothly.



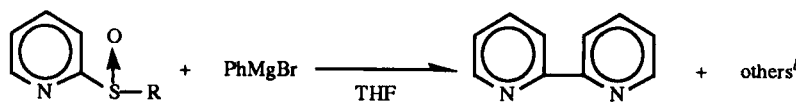







SCHEME 6. Ligand coupling reaction.

TABLE I
PREPARATION OF BIPYRIDYLS

X	R	R'M	Solvent	Time	% Yield
H	Me	MeMgBr	THF	15 min	73
H	Me	EtMgBr	THF	15 min	57
H	Me	EtMgBr	Et ₂ O	15 min	30
H	Me	PhMgBr	THF	15 min	79
H	Me	2-Pyridyl-Li	THF	15 min	59
H	Me	EtMgBr	THF	15 min	55
H	Ph	EtMgBr	THF	15 min	42
H	2-Pyridyl	EtMgBr	THF	15 min	63
Cl	Me	MeMgBr	Et ₂ O	12 hr	24
Cl	Me	EtMgBr	THF	12 hr	33
Cl	Me	EtMgBr	Et ₂ O	1 hr	55
Br	Me	EtMgBr	Et ₂ O	1 hr	50
SMe	Me	EtMgBr	Et ₂ O	1 hr	61

TABLE II
COUPLING REACTIONS OF PYRIDYL SULFOXIDE WITH PhMgBr

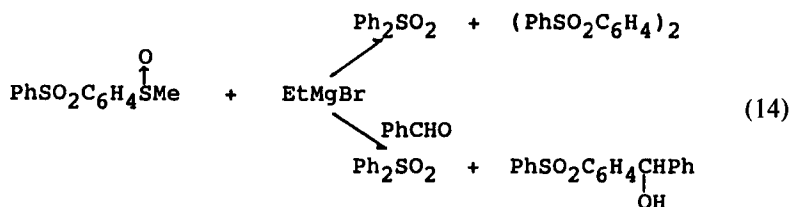
			
R	PhBgBr (mole ratio)	% Products Obtained	
		Bipyridyl	Others
Me	0.5	79 ^a	PhS(O)Me 36 ^a
Me	1.0	78 ^a	PhS(O)Me 39 ^a
Me	1.0	68	PhS(O)Me 30 PhSMe 23
			 9
			 4
Et	0.5	56	PhS(O)Et 30 PhSS(O)Et 8
			 6
Et	1.0	56	PhS(O)Et 52 PhSEt 20
			 17
<i>i</i> -Pr	1.0	59	PhS(O)Pr- <i>i</i> 42 <i>i</i> -PrSS(O)Pr- <i>i</i> 23
			 85
<i>t</i> -Bu	1.0	0	<i>t</i> -BuSS(O)Bu- <i>t</i> 63

^a By gas-liquid chromatography analysis. In all reactions, 2-alkylpyridine was not obtained.

^b Reaction time was 15 min; the reaction occurred at room temperature.

This is a very convenient method for preparing various 6,6'-substituted 2,2'-bipyridyls (Table I) (87PS123). It is interesting to see the change in a yield of 2,2'-bipyridyl when the R group changes from methyl to *t*-butyl (Table II) (87PS123). As the bulkiness of the R group increases, direct coupling between 2-pyridyl and the phenyl group starts to compete with the consecutive reactions of ligand exchange and coupling. When R becomes *t*-butyl, the only reaction occurring is the direct coupling between 2-pyridyl and the phenyl group. This is expected mainly because of the bulky *t*-butyl group, which is placed at an axial position rather than at an

equatorial position where the readily exchangeable 2-pyridyl group is placed for facile ligand coupling. Another example of this is shown in reaction (14) (88TL4441). The ease of ligand exchange does not seem to be



associated with the electron-withdrawing property of the ligand since the electron-withdrawing property of the benzenesulfonyl group is much lower than that of the 2-benzothiazolyl group, which is even higher than the 2-pyridyl group. Here again, in the presence of benzaldehyde, the benzenesulfonylphenyl group is trapped in excellent yield, as shown in reaction (14) (87MI2). The 2-thienyl group, considered to be as electron-withdrawing as a 4-pyridyl or benzenesulfonylphenyl group as diagnosed by ^{13}C -NMR chemical shifts, is another ligand which undergoes predominant ligand exchange even in the reaction of benzyl 2-thienyl sulfoxide with Grignard reagents (87MI2).

In the examples shown in Scheme 6, methyl 2-pyridyl sulfoxide reacts with Grignard or organolithium reagents to initially afford 2-pyridylmagnesium bromide, which must be a ligand-exchange product derived from the reaction on the sulfur atom. However, pyridylmagnesium bromide reacts rapidly with the original sulfoxide and is detected only by trapping with benzaldehyde. Actually, 2-pyridylmagnesium bromide has reportedly been produced by the normal method using 2-halopyridine with magnesium metal in THF or anhydrous ether [40RTC971; 44JCS276; 48JOC502; 69AG(E)279]. However, these reported procedures do not give reproducible results and are considered ambiguous. Thus, the present ligand exchange procedure is the most convenient process for preparing pyridyl or other heteroaryl Grignard reagents. In attempts to generate the pyridyl Grignard reagents, various sulfoxides having at least one pyridyl and aryl group were subjected to Grignard reagents to give the corresponding 3-, or 4-pyridyl or 4-quinolyl Grignard reagents, which were then trapped by treating them with carbonyl compounds (86TL3899). The results are shown in Table III. However, the 2-pyridyl Grignard reagent was not obtained even by this procedure, which resulted in the formation of 2,2'-bipyridyl as a major product. The ligand-exchange reactions of 3- or 4-pyridyl (or 4-quinolyl) aryl sulfoxides with, for example, PhMgBr , apparently took place via ligand exchange on the tricoordinate sulfinyl sulfur

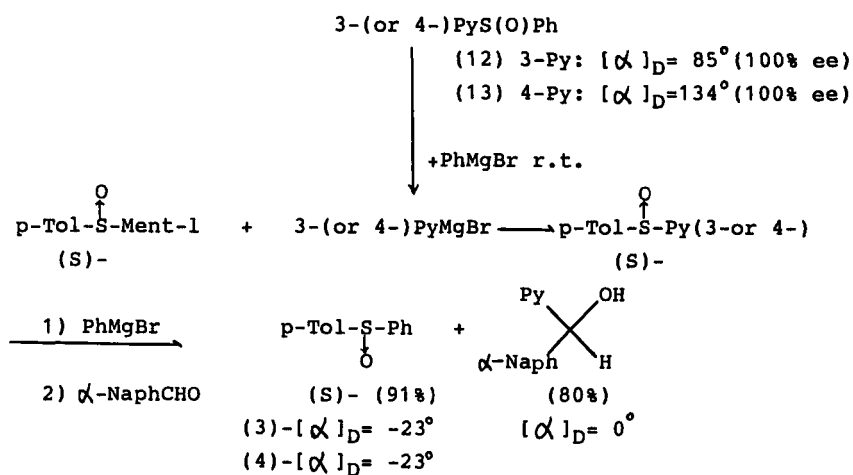
TABLE III
GENERATION OF 3- AND 4-PYRIDYL GRIGNARD REAGENTS AND REACTIONS WITH
ALDEHYDES AND KETONES

Sulfoxide	Aldehyde (or Ketone)	Alcohol	% Yield
3-PySOPh	PhCHO	Py—CH(OH)—Ph	88
3-PySOPh	α -Naph—CHO	Py—CH(OH)—Naph— α	80
4-PySOPh	PhCHO	Py—CH(OH)—Ph	64
4-PySOPh	α -NaphCHO	Py—CH(OH)—Naph— α	63
4-PySOPh	MeO——CHO	Py—CH(OH)—	73
4-PySOPh	CHO		81
4-PySOPh	PhCH=CHCHO	PhCH=CHCH(OH)—Py	60
3-PySOPh	PhCOMe	PyPh(Me)COH	47
3-PySOPh			54
3-PySOPh			61
3-PySOPh	PhCH=CHCOPh	Py(Ph)CHCH ₂ COPh	64
3-PySOPh	(PhCO) ₂ O	PyCOPh	75
4-PySOPh	PhCOMe(60°C)	PyPh(Me)COH	26
4-PySOPh	PhCOPh(60°C)	PyPh ₂ COH	7
4-PySOPh			55
4-PySOPh			38
4-PySOPh			64
4-PySOPh			66
4-PySOPh	PhCH=CHCOPh	PyPhCH—CH ₂ COPh	60
4-PySOPh	(PhCO) ₂ O	PyCOPh	70
4-PySOPh	PhCOCl	PyCOPh	24
4-PySOPh	PhCO ₂ Et(60°C)	No reaction	0

^a Reaction time was 15 min; the reaction occurred at room temperature.

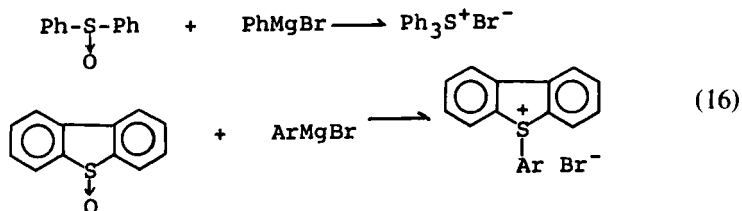
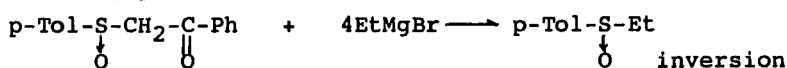
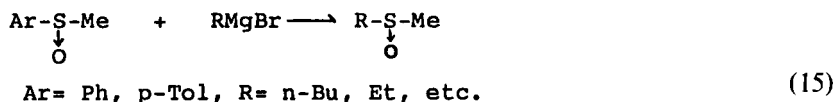
atom. The mechanism of this ligand exchange was investigated stereochemically using the reaction of optically active 3- or 4-pyridyl to tolyl sulfoxide with PhMgBr; the reaction was found to proceed via a complete inversion process on the sulfur atom. (86TL3899). In this reaction, the sulfuran was expected to be formed, as in the reactions of many other sulfoxides with Grignard or organolithium reagents (73S485; 74CJC761; 77S789). However, the reaction was so short-lived, only the Walden inversion product resulted without pseudorotations. The optically active sulfoxides were prepared according to the modified Andersen's procedure starting with (-)-*p*-tolyl menthylsulfinates and 3- or 4-pyridyl Grignard reagent, which was generated by the ligand exchange procedure of the corresponding sulfoxides (12) and (13) as described earlier (62TL93). The results are shown in Scheme 7.

In this reaction, if it is assumed that the ligand exchange proceeds via an inversion process, (*S*)-pyridyl sulfoxides (12) and (13) should also give (*S*)-phenyl *p*-tolyl sulfoxide upon treatment with phenylmagnesium bromide. Apparently, this ligand exchange of Grignard reagents proceeds via the Walden inversion on the sulfur atom. Thus, this Grignard exchange procedure is useful not only for the syntheses of optically active sulfoxides bearing heteroaromatics, but also for providing heteroaryl Grignard reagents. Unfortunately, there have been only a few reports on the preparation of optically active sulfoxides of azaheterocycles. One is the application of the Sharpless oxidation by Kagan and co-workers (84JA8188). Another is the resolution of 1-menthyl-2-pyridylpropenic acids reported by Koizumi and co-workers (85TL6205). Many other examples of the



SCHEME 7

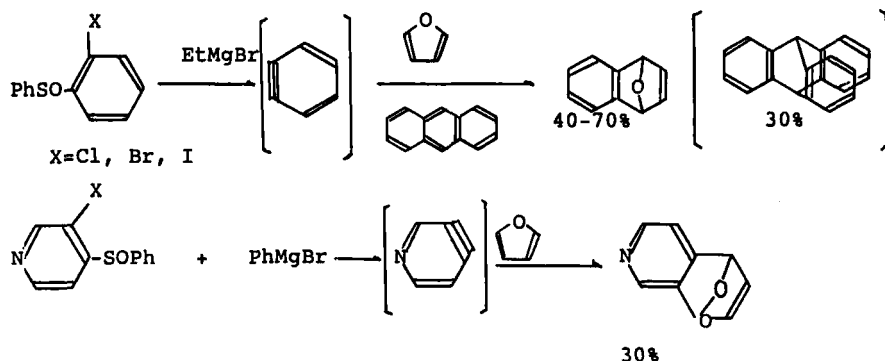
Grignard exchange reactions of sulfoxides substituted with groups other than azaheterocycles proceed mostly by an inversion on the sulfur atom; there are a few exceptions (73S485; 74CJC761). As shown in reactions (15) and (16), optically active dialkyl sulfoxides can be prepared starting from



diaryl or alkyl aryl sulfoxides and Grignard or organolithium reagents (77CL249). In these ligand exchange reactions, electropositive ligands are usually replaced by an alkyl group with complete inversion. The ligands thus exchanged have not been well characterized except in the case of pyridyl and *p*-benzenesulfonylphenyl groups. Meanwhile, diaryl sulfoxides have been known to react with aryl Grignard reagents to afford the corresponding sulfonium salts in which the oxygen atom becomes a leaving group (70JOC706; 74JOC964). This preferential attack of the Grignard reagents on the sulfinyl sulfur atom of the sulfoxides has also been used to generate benzyne and pyridyne (87TL2727). When *o*-halophenyl (or halo-pyridyl) phenyl sulfoxides are treated with the appropriate Grignard reagents, benzyne or 3,4-pyridyne is generated and trapped by adding furan or anthracene as shown in Scheme 8.

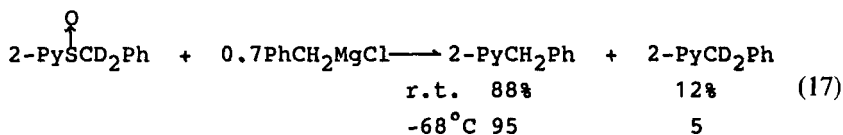
D. LIGAND COUPLING AND PSEUDOROTATION

In the reaction of benzyl 2-pyridyl sulfoxide with either alkyl or aryl Grignard reagents, or in the reaction of 2-pyridyl alkyl or aryl sulfoxides with benzylmagnesium halide, ligand coupling always takes place between the 2-pyridyl and benzyl groups. This may mean that regardless of the incoming nucleophile, which approaches the sulfur atom from an axial direction, pseudorotation always puts a 2-pyridyl group at an equatorial



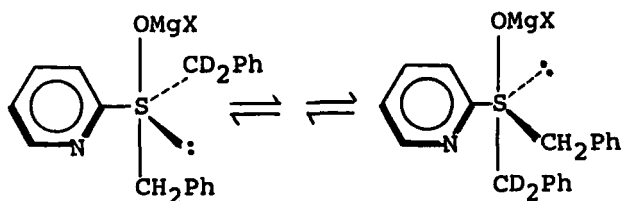
SCHEME 8. Generation of benzyne and pyridyne.

position and a benzyl group at an axial coordinate for facile ligand coupling. However, there are cases in which ligand coupling proceeds faster than pseudorotation, as shown previously in the reaction of *N*-*p*-tosyldiphenylsulfilimine with phenylmagnesium bromide by our ^{14}C -tracer experiment (72BCJ2019). Another example may be our finding (84TL69), in reaction (17), where the incoming benzyl group couples preferentially



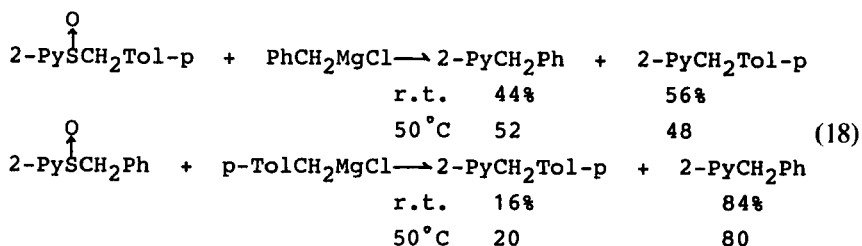
with the 2-pyridyl group. In order for 2-pyridyl and benzyl- D_2 groups to couple, the original sulfoxide has to undergo pseudorotation from reaction (14) to reaction (15). However, in the latter reaction, especially at a higher temperature, $\sim 50^\circ\text{C}$, pseudorotation seems to occur relatively faster than ligand coupling.

In the similar reaction of 2-pyridyl benzylic sulfoxides with benzylic Grignard reagents, the incoming benzylic group seemed to couple pref-

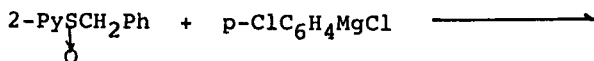
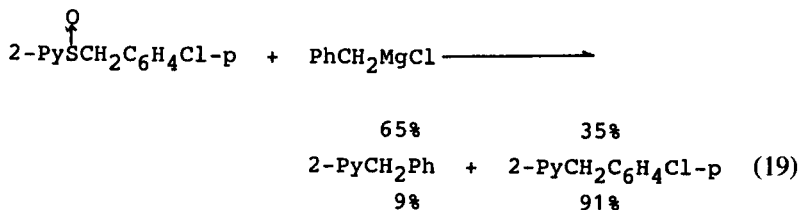


SCHEME 9. Pseudorotation.

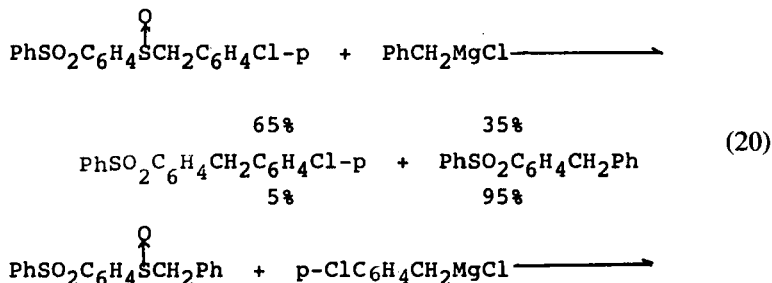
entially with the 2-pyridyl group. Here again, pseudorotation seems to be accelerated more than the coupling as the temperature increases [reaction (18).] However, substitution of an electron-withdrawing chlorine



atom at the *p*-position of a benzyl group alters the situation, 2-*p*-chlorobenzylpyridine becomes the major product [reaction (19)]. When a 2-pyridyl

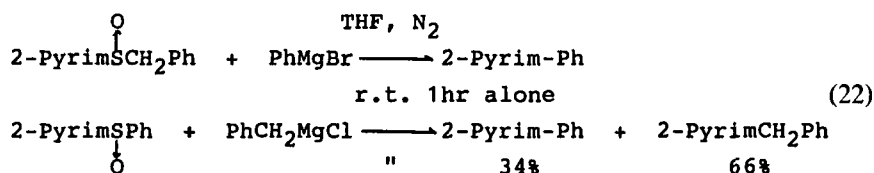


group was replaced by a *p*-benzenesulfonylphenyl group, ligand coupling seemed to take place between the *p*-benzenesulfonylphenyl group and the benzylic group bearing the more electron-withdrawing substituent, [reaction (20)] (88TL4441).

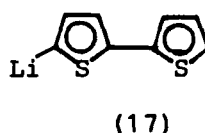
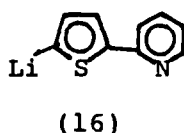


In the reactions of 2-pyridyl sulfoxides with Grignard reagents (71CC649), benzylic groups tended to couple preferentially with the *p*-

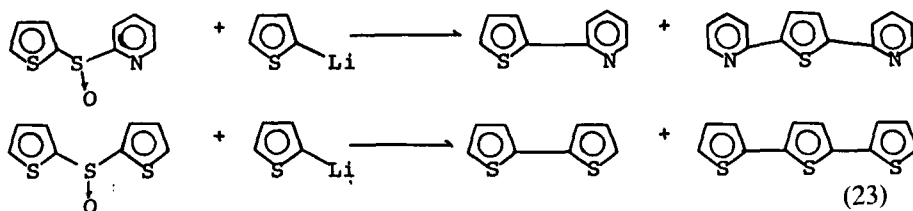
2-pyridyl group; it tends to couple preferentially with a benzyl group over a phenyl group in the reaction of benzyl 2-quinolyl sulfoxide with a phenyl Grignard reagent, or in the reaction between 2-quinolyl phenyl sulfoxide with benzylmagnesium chloride. However, 2-benzylquinoline was obtained along with a small portion of 2,2'-biquinolyl in the reaction of 2-quinolyl phenyl sulfoxide with the ethyl Grignard reagent. 2-Phenylquinoline was obtained in a good yield together with 2,2'-biquinolyl when phenyl 2-quinolyl sulfoxide was treated with the phenyl Grignard reagent [88H(ip)1, 88TL(ip)1; 88TL(ip)2]. Another interesting case involves 2-pyrimidyl sulfoxides [reaction (22)]. Apparently, a 2-pyrimidyl group



tends to couple preferentially with a phenyl group over a benzyl group, which is the most favored ligand to couple with other heteroaromatic groups. Indeed, the treatment of alkyl 2-pyrimidyl sulfoxides with the phenyl Grignard reagent is a convenient way of preparing 2-phenylpyri-

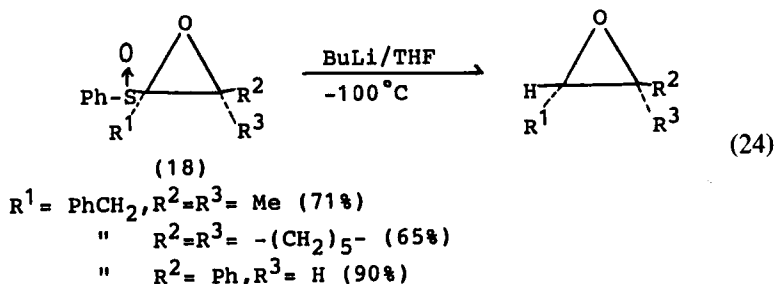


midine. The following two reactions are also interesting examples. The former involves intermediate **16**, the latter involves intermediate **17**, (88MI1), [reaction (23)].



Some other desulfinated ligand-exchange or ligand-coupling reactions have been reported in which α , β -epoxysulfoxides (**18**) (86TL2379; 87TL2603) and vinylic or allenic sulfoxides (87TL6565) were used with alkyl lithium reagents. When the α , β -epoxides bearing an α -sulfinyl group react with one equivalent of BuLi at -100°C in THF, desulfination was

observed to give stereospecifically the corresponding epoxides in high yields [reaction (24)]. This reaction is considered to proceed via an initial

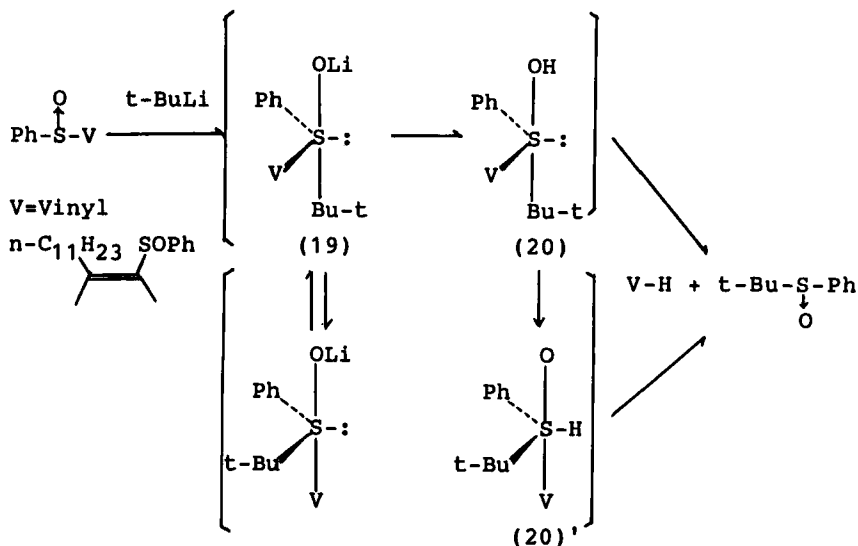


attack of BuLi on the sulfinyl sulfur atom to give the sulfurane as an incipient intermediate.

Okamura and co-workers treated vinylic or allenic sulfoxides with *t*-BuLi and MeOH in THF to give the corresponding desulfinated products in high stereoselectivities. In these reactions, formation of vinyl or allenyl lithium was assumed to take place by the attack of *t*-BuLi on the sulfur atom of the sulfoxides. However, upon quenching the reaction mixture with electrophiles such as alkyl iodides or $(\text{CH}_3)_3\text{SiCl}$, the corresponding alkyl-substituted products were not obtained. Thus, it was proposed that the reactions of vinylic or allenic sulfoxides with *t*-BuLi initially give the sulfurane (19) as the intermediate and not the free vinyl or allenyl lithium. Sulfurane (19) abstracts a proton from the solvent to give a new hypervalent species (20), and the subsequent ligand coupling within 19 gives the vinylic compound and *t*-butyl phenyl sulfoxide with a high stereoselectivity (Scheme 10).

The scope and limitations of this coupling reaction within the hypervalent species have not yet been thoroughly scrutinized. However, in the reaction of sulfoxides with Grignard reagents, we expect not only a pyridyl group, but also other heteroaryl groups, such as 2-thienyl and 2-furyl groups, to undergo ligand coupling based on our crude diagnosis of possible reactions using ^{13}C -NMR. This crude diagnosis reveals that benzylic or allylic groups as well as vinylic and electron-releasing alkyl groups such as ethyl and *t*-butyl groups can couple within the incipient σ -sulfurane formed in the reactions of sulfoxides with Grignard reagents. Indeed, *t*-butyl and isopropyl groups have been shown to couple with the 2-pyridyl group in the reaction of alkyl 2-pyridyl sulfoxides with the respective Grignard reagents (87PS139).

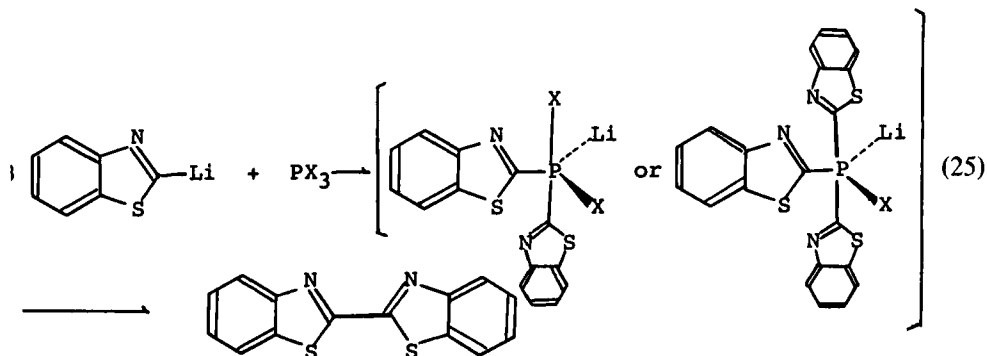
The concept of ligand coupling within hypervalent intermediates can be widely applied not only to the reactions of organic sulfur compounds with nucleophiles, but also to many of those in which the central heteroatoms



SCHEME 10. Coupling reaction of sulfoxide.

can expand their valence shell upon nucleophilic attack. For example, 2,2'-bipyridyl forms nicely when tri-2-pyridylphosphine oxide is treated with either Grignard reagents or even acidic media. (89TL6359).

We have found that treatment of 2-lithiobenzothiazole with trihalophosphines readily affords bis-di(2,2'-dibenzothiazyl) as shown in Reaction (25). This is another interesting example of a ligand-coupling reaction



(90H347). The reaction of Gilman's reagent, R_2CuLi , also involves ligand coupling. There are many examples of hypervalent iodine compounds.

Many of those examples involving ligand coupling within hypervalent species have been documented (86MI1, 86PS13; 88MI1).

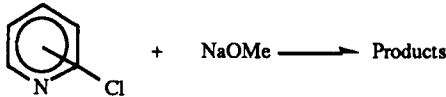



III. Ipso-Substitution of Azaaromatic Sulfoxides and Sulfones

A. INTRODUCTION TO IPSO-SUBSTITUTION

As described in the previous section, azaaromatic sulfoxides react with organometallic reagents on the sulfinyl sulfur atom to initially form an incipient intermediate, σ -sulfurane, which immediately undergoes either ligand exchange or ligand coupling to give the final products. In general, halobenzenes and their derivatives undergo ipso substitution reactions when treated with various nucleophiles. However, the halobenzenes used in the reactions for ipso substitution are required to have strong electron-withdrawing substituents such as nitro and sulfonio groups. Otherwise, the reaction must be carried out in the presence of copper or other metals used as catalysts (58QR1; 60AG294; 64CRV613; 77Mi4). Meanwhile, when halobenzenes bearing no other electron-withdrawing groups are treated with strong bases such as NaNH_2 in liquid NH_3 , benzyne species are formed as intermediates which then gives an amide anion as the products [53JA3290; 57CI(L)80; 60AG91; 64CB3268; 65AG(e)731; 68BCJ1463; 78MI1]. The sulfinyl or sulfonyl group can serve as the leaving group in nucleophilic reactions of benzene derivatives bearing a nitro group [53JA3290; 57CI(L)80; 60AG91; 64CB3268; 65AG(E)731; 68BCJ1463; 78MI1]. Azaaromatic compounds also undergo nucleophilic aromatic substitutions with nucleophiles or bases, and various substituents on the rings serve as leaving groups. For example, not only halogen but also sulfur functional groups, a nitro group, and even a hydrogen atom serve as the leaving group.

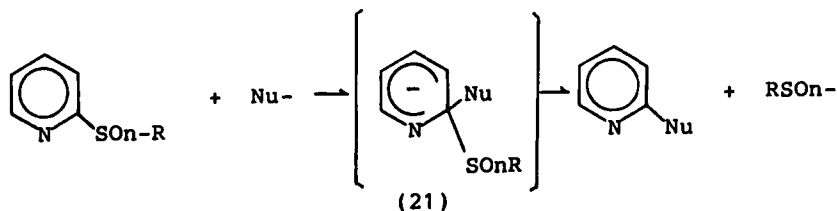
Illuminati wrote a pioneering review article on the nucleophilic aromatic substitution reactions on the azaaromatics (58AJC297; 64AHC285). A more elaborate review was presented by Buncl *et al.* (84MI5). These reviews and others have demonstrated that many azaaromatics are highly electron-withdrawing, e.g., a pyridyl group is as highly electron-withdrawing as a nitrophenyl group. Comparison of the rates of the nucleophilic aromatic substitution reactions of various halopyridines and their *N*-oxides and *N*-methylpyridinium salts with MeONa in MeOH to the rates of chlorobenzene, taken as a reference to be 1.0, is shown in Table IV (64AHC285). The rates of nucleophilic substitution increase enormously by converting pyridine derivatives to the corresponding *N*-oxides or pyridinium salts. In the previous section, the sulfinyl sulfur atom in pyridines and

TABLE IV
RELATIVE REACTIVITY OF PYRIDYL DERIVATIVES IN NUCLEOPHILIC
AROMATIC SUBSTITUTIONS

		
Position of Cl	Relative rate of Reaction (mol s ⁻¹)	
Cholorobenzene	1.0	
	2-	2.76×10^8
	3-	9.12×10^8
	4-	7.43×10^9
	2-	5.30×10^{12}
	3-	9.67×10^9
	4-	8.33×10^{12}
	2-	1.28×10^{21}
	3-	2.62×10^{13}
	4-	4.23×10^{19}
<i>p</i> -NO ₂ C ₆ H ₄ Cl	7.10×10^{10}	

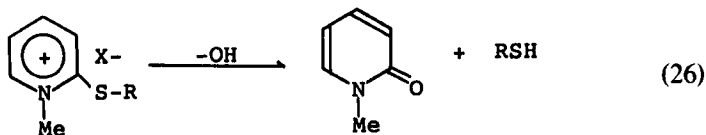
related azaaromatics is shown to be attacked by organometallic reagents. 2- and 4-Sulfinylpyridines also react with other common nucleophiles such as OH⁻, RS⁻ to give the corresponding ipsosubstitution products. Furthermore, the sulfonyl group in 2- or 4-pyridyl sulfone is also readily replaced by the common nucleophiles, including Grignard reagents, to give the corresponding ipsosubstitution products upon heating. In aromatic nucleophilic substitutions using *p*-nitrophenyl derivatives, the leaving ability has been reported to fall in the following order (77MI4), F > NO₂ > OTs > SPh > Cl~Br~I~NR₃ > OAr > OR > SR > SO₂ > R > NH₂.

Interestingly, the nitro group is one of the best leaving groups. However, the sulfonyl group in the *p*-position of a nitrobenzene is not substituted at all under the same reaction condition. Contrary to this, in the nucleophilic substitution reactions of common azaaromatic compounds, sulfonyl, sulfinyl and even the ammonio groups are better leaving groups than chloride. The leaving ability of the sulfonyl or sulfinyl group depends on the nature of the azaaromatic; these sulfur groups are replaced by common nucleophiles ~100 times faster than chloride. Therefore, Barlin,



SCHEME 11. Ipsso-substitution.

Brown, and co-workers concluded that the reaction proceeds via formation of a Meisenheimer-type complex (21) in the rate determining step (Scheme 11) [66AJC1487; 67JCS(B)568, 67JCS(C)568, 67JCS(C)2473; 69JCS(B)333, 69JCS(C)921; 72JCS(P1)1269]. According to their results, the rate of the reaction increases, increasing the number of nitrogen atoms in the azaaromatics. Even the sulfinyl group is substituted by OH^- in EtOH, though the sulfinyl group is generally considered to be inert to the common nucleophiles under the reaction conditions employed for the substitution of the sulfinyl or the sulfonyl groups by the OH^- ion in EtOH (60CB1590; 69KGS677). The sulfinyl group attached to the pyridinium salts is removed quite readily and hence the reactions are used for the preparation of thiols as shown in reaction (26) (77JOC2180; 88BCJ247).

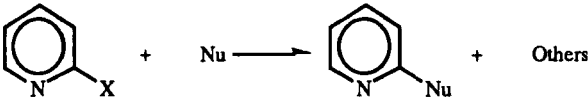


The facile leaving ability of the sulfinyl or the sulfonyl group attached to these azaaromatics as compared to the leaving ability of chloride and bromide suggests that the formation of a Meisenheimer-type complex is the rate-determining step, and the sulfinyl and the sulfonyl groups are more electron-withdrawing and thereby stabilize the Meisenheimer-type complex resulting in facile replacement. Thus, the reactions are quite useful for preparing azaaromatics having various functional groups, since sulfur functional groups can readily be introduced into the azaaromatic rings [on the preparation of the sulfur compounds, see, for example, Rodds (76MI2)] One useful application of this facile ipsosubstitution is that different substituents can be introduced regioselectively onto azaaromatics bearing both the halogen atom and the sulfinyl or sulfonyl group at appropriate positions. These substituted azaaromatics are subjected to nucleophilic reactions. Under ordinary conditions, the sul-

finyl or sulfonyl group is initially replaced by one nucleophile, and only under more severe conditions does the second nucleophile substitute the halogen atom. Several examples of the ipso substitution of 2-, 4-, and 2,6-disubstituted pyridine derivatives are shown in Table V [67JCS(B)568; 69JCS(B)333; 84JCS(P1)1839].

These reactions were applied to the preparation of macrocycles containing pyridine and other heterocycles as shown in Scheme 12 [84JCS(P1)1833]. The starting material for this synthesis is 2,6-dichloropyridine which was converted to 2-chloro-6-methylthiopyridine quantitatively when the reaction was carried out under a liquid-liquid binary phase

TABLE V
REACTIONS OF SULFUR COMPOUNDS WITH NUCLEOPHILES

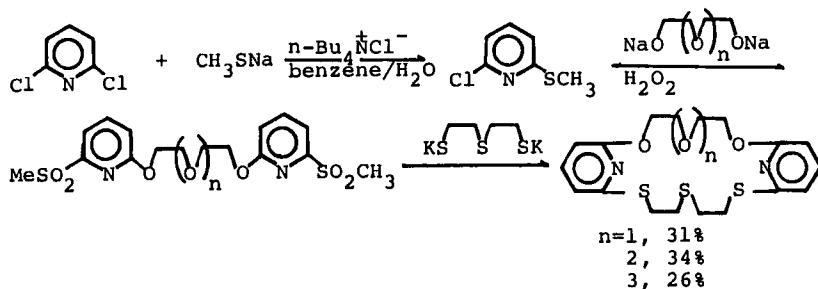
						
Substrates X	Nucleophile	Solvent	Temp.(°C) ^a	Time(hr)	% Product Yields	
					Ipso	Others
2-SMe	EtONa	EtOH	Reflux	5	— ^d	— ^d
4-SMe	EtSNa	EtOH	Reflux	5	— ^d	— ^d
2-S(O)Me	MeONa	MeOH	120	3	77	
2-S(O)Me	EtONa	EtOH	50	2	73	Sulfide, 8
2-S(O)Me	EtSNa	EtOH	50	5	74	Sulfide, 18
2-S(O)Me	PhSK	t-BuOH	Reflux	5	47	Sulfide, 7
2-S(O)Me	PhOK	t-BuOH	Reflux	18	— ^d	— ^d
2-S(O)CH ₂ Ph	EtONa	EtOH	Reflux	1.5	80	
4-S(O)Me	MeONa	MeOH	80	6	87	
4-S(OH)Me	EtONa	EtOH	Reflux	3	63	Sulfide, 21
2-Cl-6-S(O)Me	EtONa	EtOH	50	1	74	Sulfide, 13
2-Cl-6-S(O)Me	EtSNa	EtOH	RT	1.5	68	Sulfide, 20
2-S(O) ₂ Me	NaOH	MeOH	145	12	70	
2-S(O) ₂ Me	EtONa	EtOH	Reflux	1.5	79	
2-S(O)Ph	EtSNa	EtOH	Reflux	0.2	87	
2-Cl-6-SO ₂ Me	EtSNa	EtOH	50	1	84 ^a	
2-Cl-6-SO ₂ Me	EtSNa	EtOH	RT	1.5	90	
2-Cl-6-SO ₂ Me	EtSNa ^b	benzene	Reflux	0.25	100	
2-Cl-6-SO ₂ Me	NaCN	DMF	RT	162	94	
2-Cl-6-SO ₂ Me	NaCN	DMF	60	12	76	
4-S(O) ₂ Me	NaOH	MeOH	145	12	72	

^a Only 2-chloro-6-substituted product was obtained.

^b In the presence of 18-crown-6.

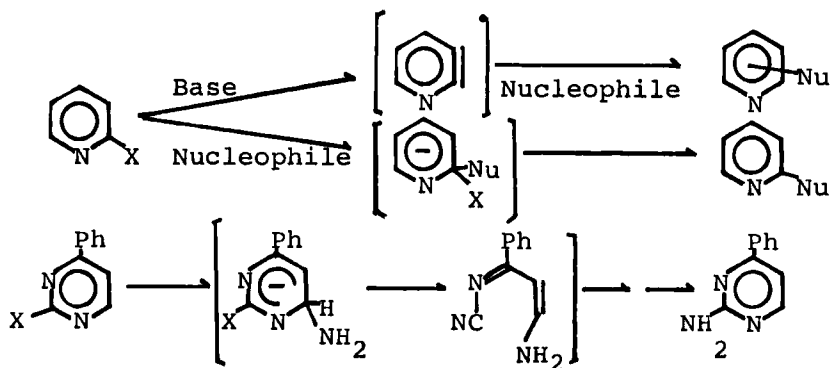
^c RT, Room temperature.

^d No Reaction.



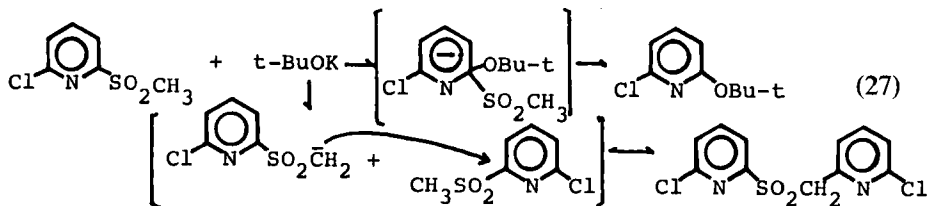
SCHEME 12. Preparation of macrocycles.

transfer condition using $n\text{-Bu}_4\text{N}^+\text{Cl}^-$ as the catalyst. Treatment of 2-chloro-6-thiomethylpyridyl sulfide with polyethylene glycol disodium salts, and subsequent treatment of the sulfide obtained with H_2O_2 or peracid, gave the corresponding sulfone bearing a 6,6'-polyethylene glycol bridge. Then, the sulfone was allowed to react with appropriate polyethylene polythiols affording the macrocycles bearing different podands. By changing the nucleophiles, appropriately substituted macrocycles can be synthesized. Therefore, this procedure is a very convenient synthetic method for preparing macrocycles bearing different podands. As a marked contrast to the above results, both primary and secondary aliphatic amines react with 2-chloro-6-methylsulfonylpyridine to give the ipsosubstitution product at the carbon atom bearing a chlorine atom, while lithium piperide reacts with the carbon atom attached to the sulfonyl group to give 2-chloro-6-piperidylpyridine exclusively. The reason for this difference in reactivity of the two reagents is probably due to the difference in stability of the Meisenheimer-type complexes formed initially. In the ipsosubstitution of the sulfonyl group, the sulfonyl oxygen coordinates with the metal cation and the pyridyl nitrogen atom to stabilize the Meisenheimer-type complex in the rate-determining step, thus facilitating the attack of the nucleophiles (84TL1549). In general, halogen atoms on the azaaromatic compounds are removed by the three different mechanistic processes: One is the elimination-addition involving a heteroaryne as an intermediate; the second is the normal ipsosubstitution; the third is the so-called ANRORC (addition nucleophile ring opening ring closure mechanism) which involves the initial addition of a nucleophile, subsequent ring opening, and ring closing, as shown in Scheme 13 (73TL1887; 76MI3; 78ACR462; 82T427). Ligand coupling may be involved, particularly with iodo compounds. (86MI1, 86PS13; 88MI1).

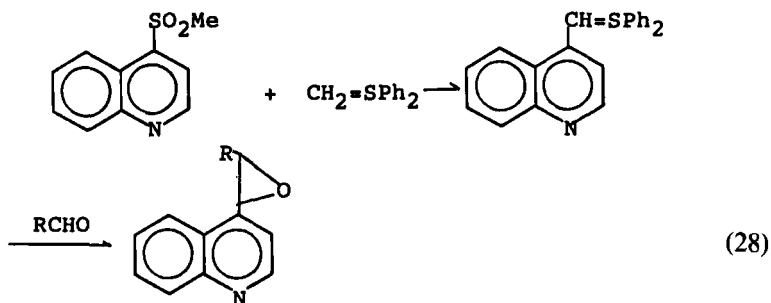


SCHEME 13. Mechanisms of heteroaromatics with bases or nucleophiles.

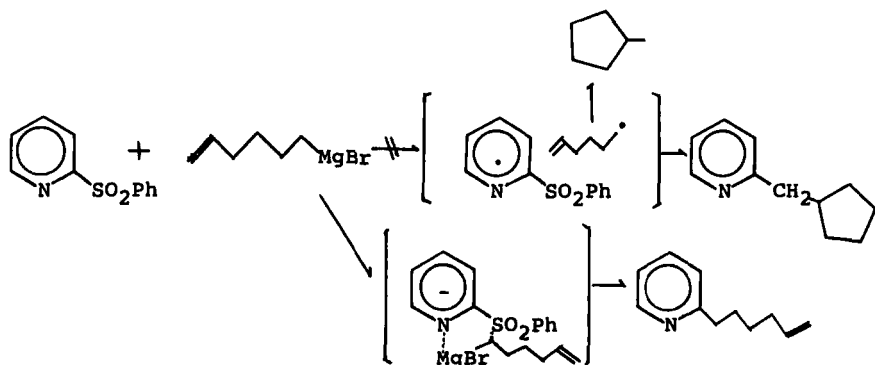
Another interesting reaction of sulfonylpyridines is with *t*-BuOK in CH_2Cl_2 , in which even a bulky alkoxide such as *t*-BuOK substitutes the sulfonyl group to give 2-*t*-butoxypyridine in substantial yield together with (6'-chloro-2'-pyridylmethyl)-6-chloro-2-pyridyl sulfone. The formation of this sulfone is accounted for by the initial formation of the sulfonyl carbanion which reacts further with the starting sulfone to afford the product [reaction (27)] (82UP2). This reaction also demonstrates that even a



carbanion can substitute a sulfonyl group more readily than a chlorosubstituent. However, other common carbanions such as sodium diethylmalonate in EtOH do not react with the sulfone. In another case, 4-methylsulfonylquinoline reacts with diphenyl sulfonium methylide to give the intermediate corresponding to substituted ylide which then reacts further with aldehydes to yield the epoxide derivatives of quinoline [reaction (28)] (66TL1123; 72JA6218). Both 2- and 4-sulfonylpyridines also react readily with numerous Grignard reagents, however, the products and the modes of reaction are quite different from those of other 2-substituted and 4-substituted derivatives (86H3337). The product obtained are summarized in Table VI.

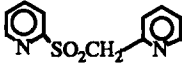




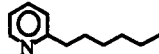
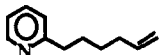
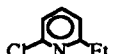
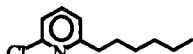
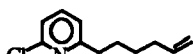
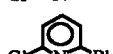
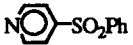
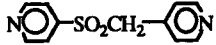
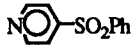

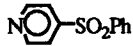

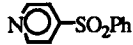
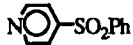
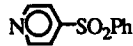


In the reaction of 2-sulfonyl substituted pyridines, the Grignard reagents directly substitute the sulfonyl group to give the corresponding ipso-substituted products in high yields. For example, the reactions of 2-chloro-6-phenylsulfonylpyridine with Grignard reagents gives 2-chloro-6-alkyl- (or aryl-) pyridine as a sole product leaving the 2-chloro group completely untouched. This is obviously a ligand coupling reaction like the reaction of phenyl 2-phenylacetylene sulfone with *n*-butyl lithium to afford 1-phenyl-2-butylacetylene (79JOC3444). Substitution of an electron-withdrawing chlorine atom at the 2-position apparently facilitates nucleophilic attack of Grignard reagents on the sulfonyl sulfur atom, eventually giving the ligand coupling product. These reactions are quite useful to prepare 2,6-disubstituted pyridine derivatives bearing different substituents (86JOC505). Another example of similar ipso-substitution is the reaction of 2-benzenesulfonylpyridine with 5-hexenylmagnesium bromide to afford only 2-(5-hexenyl)pyridine in a high yield without contamination of 2-(cyclopentylmethyl)pyridine (86H3337). The lack of 2-(cyclopentylmethyl)pyridine suggests there is no probability of an electron transfer mechanism (SET) (see Scheme 14). Benzenesulfinate is an excellent radi-



SCHEME 14. Mechanism for ipso-substitution.


TABLE VI
REACTIONS OF SULFONYLPYRIDINES WITH GRIGNARD REAGENTS

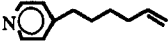
$ \begin{array}{c} \text{C}_6\text{H}_5 \\ \\ \text{N} \\ \\ \text{SO}_2\text{R} \end{array} + \text{RMgBr} \xrightarrow{\text{THF}} \text{Products}^a $					
R	R'	Time (min)	Products obtained	%Yield	% Recovered
SO ₂ Me	Ph	60		65	25
SO ₂ Ph	Ph	60		53	39
SO ₂ Ph	<i>p</i> -Tol	60		72	21
SO ₂ Ph	PhCH ₂	60		57	---
SO ₂ Ph	<i>sec</i> -Oct	120		24	---
SO ₂ Ph	<i>n</i> -Hexyl	30		95	---
SO ₂ Ph	5-Hexenyl	30		99	---
2-Cl-6-SO ₂ Ph	Et	15		79	---
2-Cl-6-SO ₂ Ph	<i>n</i> -Hexyl	30		44	---
2-Cl-6-SO ₂ Ph	5-Hexenyl	30		51	---
2-Cl-6-SO ₂ Ph	Ph	120		25	---
 -SO ₂ Ph	Ph	60		13	32
 -SO ₂ Ph ^b	Ph	240		51	10
 -SO ₂ Ph ^c	<i>p</i> -Tol	240		25	35
 -SO ₂ Ph	<i>n</i> -Dodecyl ^d	240	4,4'-bipyridyl	54	17
 -SO ₂ Ph	Et	240	4,4'-bipyridyl	28	---
 -SO ₂ Ph	5-Hexenyl	240	4,4'-bipyridyl	23	20

^aThe reactions occurred at room temperature.

^bBiphenyl was also obtained at a 65% yield.

^c*p,p'*-Bitolyl was also obtained at a 17% yield.

^d was also obtained at a 26% yield.

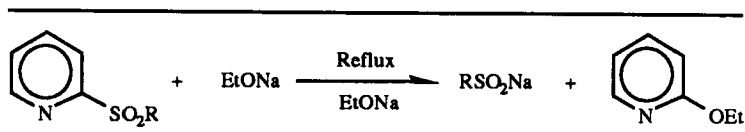
•  was also obtained at a 14% yield.

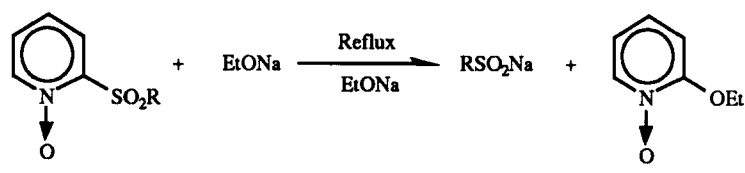
cal scavenger; thus this ipso substitution of 2-benzenesulfonylpyridine with Grignard reagents is not a SET process, though many reactions of azaaromatics with nucleophiles have been known to proceed via the SET process (83JA90).

The reaction of 4-benzenesulfonylpyridine with Grignard reagents is different from that of the 2-sulfonyl analogue and gives a complex mixture of products. In the reactions with aryl Grignard reagents, the corresponding ipso substitution takes place predominantly, whereas alkyl Grignard reagents afford both 4,4'-bipyridyl and 4-alkyl substituted pyridines in rather low yields together with intractable mixtures of products. The formation of 4,4'-bipyridyl may involve initial ligand exchange and subsequent ligand coupling. However, further experiments including stereochemical and trapping experiments are necessary to establish the reaction as a ligand coupling within the σ -sulfurane. Another advantage of this ipso substitution of sulfones is that treatment of the sulfone with suitable nucleophiles affords the corresponding sulfinic acids in high yields together with the ipso substitution products. Since a variety of alkyl or aryl-2-pyridyl sulfones can readily be prepared by oxidizing the corresponding sulfides, this ipso substitution is one of the convenient and versatile procedures for preparing sulfinic acids (86H3019). However, secondary or tertiary 2-alkyl sulfones react with NaOCH_3 slowly, affording the sulfinic acids in low yields. Therefore, the reaction requires higher temperatures or prolonged reaction times. Since it is well known that the nucleophilic ipso substitution reactions of halopyridine-*N*-oxides proceed much faster than those of the corresponding pyridine (64AHC285), one can anticipate that benzenesulfonylpyridine-*N*-oxide will be more reactive. Moreover, pyridyl sulfides were converted to *S*-oxides which then were subjected to NaOCH_3 . The results summarized in Table VII are more promising for a general preparation of sulfinic acids than the reactions using 2-pyridyl sulfones.

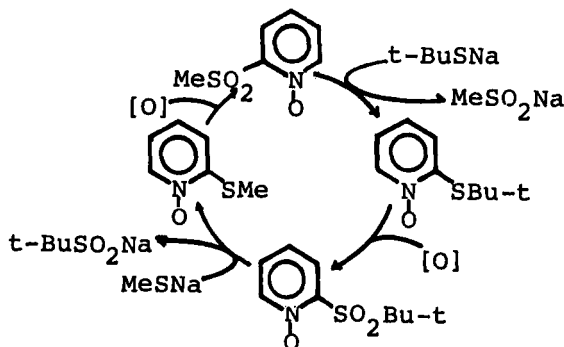
Using these procedures, not only primary but also secondary and even tertiary sulfones such as 2-(*t*-butyl)sulfonylpyridine-*N*-oxide undergo facile ipso substitution at the carbon atom bearing the sulfonyl group to give the corresponding sulfinic acids in high yields. Furthermore, 2-methylsulfonylpyridine-*N*-oxide, prepared using the $\text{S}_{\text{N}}2$ reaction of 2-mercaptopyridine-*N*-oxide with MeI , and subsequent oxidation with H_2O_2 , becomes the starting material for any kind of sulfinic acid which can be obtained in turn by treating 2-methylsulfonylpyridine-*N*-oxide with numerous thiols under alkaline conditions. In general, 2-*t*-butylsulfonylpyridine cannot be prepared by the normal $\text{S}_{\text{N}}2$ reaction. However, this ipso substitution gives *t*-butyl sulfinic acid quantitatively and 2-methylsulfonylpyridine-*N*-oxide is recovered after treating the sulfone

TABLE VII
 PREPARATION OF SULFINIC ACIDS

			
R	Ratio ^a	Time (hr)	% Yield (RSO ₂ Na)
Me	1:3	0.25	58 ^b
<i>i</i> -Pr	1:1	1	No reaction
<i>i</i> -Pr	1:2.5	48	38
PhCH ₂	1:3	0.25	52
Ph	1:3	0.25	65
Ph	1:1	19	92 ^c

				
R	Ratio	Time (min)	% Yield	
			(RSO ₂ Na)	(RSO ₂ Me)
Me ^e	1:1	10	Quant.	---
<i>n</i> -Oct	1:1	30	Quant.	83
<i>i</i> -Pr	1:1	15	Quant. ^f	---
<i>i</i> -Pr ^e	1:1	15	Quant.	---
<i>t</i> -Bu	1:1	15	Quant.	---
PhCH ₂	1:1	15	Quant.	79
Ph	1:1	15	89	68
Ph ^e	1:1	15	69	---

^a Ratio = sulfone : EtONa^b The yield of 2-ethoxypyridine was 52%.^c PhSO₂Na + MeI → PhSO₂Me, 73% yield.^d RSO₂Na + MeI → RSO₂Me.^e The yield of 2-ethoxypyridine-*N*-oxide was 95%.^f In CH₃CN at room temperature.^g 4-Phenylsulfonylpyridine-*N*-oxide in CH₃CN at room temperature.

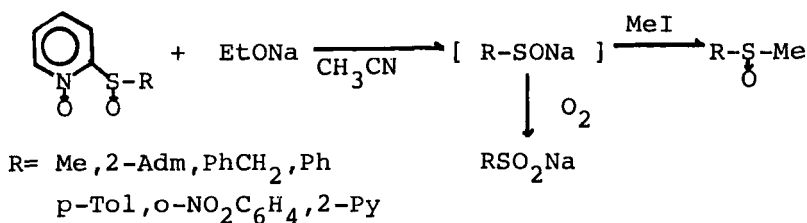


SCHEME 15. N-oxide as a mediator.

with MeSNa in MeOH. Thus, 2-methylsulfonylpyridine-*N*-oxide can be used as a mediator in the preparation of any kind of sulfinic acid as shown in Scheme 15.

A similar convenient preparation of sulfinic acids using benzothiazole derivatives has been reported (84CL2125). The sulfinyl group in pyridyl derivatives can also serve as a good leaving group as can the sulfonyl group in the ipso substitution reactions described earlier. Sulfinic acids are known to be interesting unstable species and can be prepared in isolated form only as a few compounds which are stabilized either by hydrogen bonding or by being sterically hindered [12CB2965; 72AX(B)55; 73IJS205; 74JA1609; 83JA7172]. However, all these sulfinic acids have been prepared in the form of sulfenates by treating 2-sulfinylpyridine-*N*-oxides with NaOCH₃ in EtOH solution (89CL1501). Actually several sulfinic acids have been prepared as sodium salts in solution but are usually quite sensitive to air oxidation and quickly convert to the corresponding sulfinic acids. Under careful conditions that rigorously exclude air or oxygen, sulfinic acids are generated *in situ* in the solution. Formation of sulfinic acids as sodium salts can be demonstrated by treating the solution with MeI to afford the corresponding methyl sulfoxides as shown in Scheme 16.

2-Pyridyl sulfinic acid was actually synthesized by Davis using flash vacuum pyrolysis of *t*-butyl 2-pyridyl sulfoxide and then trapping the acid on a cold finger (80JA7967). However, on warming, the acid was converted to 2,2'-dipyridyl disulfide and, unexpectedly hydrogen peroxide, which was identified using the starch-iodine method. Most sulfinic acids, when isolated, dimerize to the corresponding thiolsulfonates by facile dehydration. Therefore, 2-pyridyl sulfinic acid behaves abnormally. The mechanism for forming hydrogen peroxide has not yet been clarified, however, the strong hypervalent-type interaction between intermolecular sulfinyl sulfur atoms in the two hydrogen-bonded pyridylsulfinic acid may be



SCHEME 16. Formation of sulfenic acids.

responsible. Formation of several heterocyclic sulfenic acids has been reported and their important roles in metabolism or oxidoreduction in bioorganisms have been suggested (76ACR293; 86JOC1033). More detailed investigations on the physical and chemical properties of these sulfenic acids are expected.

B. GENERAL REACTIONS OF AZAAROMATICS WITH ORGANOMETALLIC REAGENTS AND NUCLEOPHILES

Pyridine itself is known to react with strong bases, such as NaNH_2 in liquid NH_3 , to afford 2-aminopyridine; the Chichibabin reaction (14MI1; 66AHC292). Furthermore, various organolithium and Grignard reagents also react with pyridine, quinoline, and other azaaromatic compounds to give 2- and/or 4-substituted pyridine derivatives (30JA2845; 71JA1294; 73CL1307; 75JOC569). In these reactions, the hydride ion appears to behave as a leaving group. Actually, in all cases, the reaction seems to proceed in the presence of an electron-accepting group such as carbonyl or halogen atoms. The yields and regioselectivities of the products depend markedly on reagents and conditions. Several typical examples are shown in Scheme 17 and Table VIII.

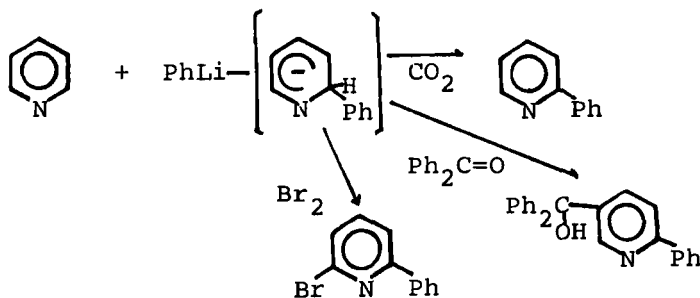
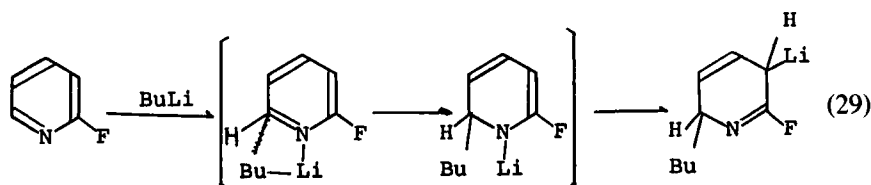
SCHEME 17. Reaction of pyridine with PhLi .

TABLE VIII
REACTIONS OF PYRIDINE WITH ORGANOMETALLIC REAGENTS



RM	% Products	
	2-	4-
<i>n</i> -BuMgI	18	---
<i>s</i> -BuMgBr	6	3
PhCH ₂ MgBr	1.5	6.5
PhMgBr	44	---
PhLi	60	---
Quinoline + PhMgBr	66	---
Quinoline + <i>n</i> -BuLi	50-90	---

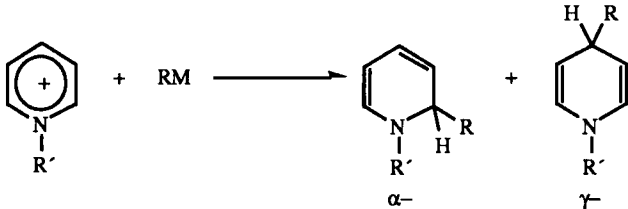



In these reactions, the most reliable mechanism is considered to involve the initial metal-coordination at the nitrogen atom of the pyridine ring and the subsequent attack of an alkyl or aryl anion at the most probable cationic sites on the ring, namely, the 2- and/or 4-position of the ring. If a 2-halogen substituted pyridine is used, the nucleophilic anion attacks the 6-position. Thus, the addition is a more preferred reaction than the ipso-substitution as shown in reaction (29). The substitution of amide or phenyl-

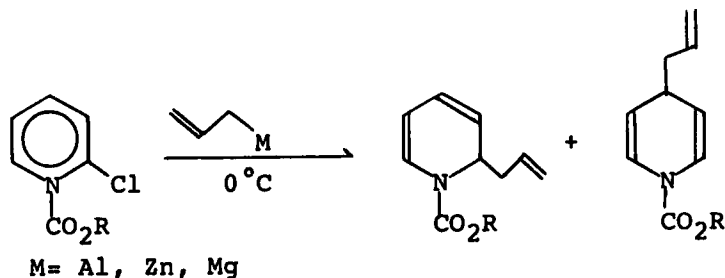


lithium at the 2-position may proceed via an ionic process and usually requires an electron-accepting compound, while many of the substitutions with nucleophiles at the 4-position are considered to be free radical processes involving a one-electron transfer such as the S_{RN}1 process, e.g., the reaction of 4-nitropyridine or its *N*-oxide with nucleophiles. A number of such reactions involving the formation of free radicals at the 4-position in the pyridine ring have been reported, and some of these free radicals have been detected by the electron spin resonance ESR technique [76JCS(P1)1977; 82JOC599]. These reactions are quite useful for the synthetic introduction of an alkyl or aryl moiety onto the 2- or 4-position of a pyridyl or quinolyl ring. However, direct treatment of pyridine with organometallic reagents usually leads to ambiguous regioselectivity and

product distribution unless modified. Therefore, several approaches have been used to introduce an alkyl or aryl moiety onto the appropriate position of heteroaromatics (74JOC59; 81JOC2213; 85TL275). If *N*-ethoxycarbonylpyridinium salts are treated with an appropriate Grignard reagent, the 4-substituted derivatives are obtained selectively in the presence of CuI. When the reaction is carried out in the absence of CuI, the 2-isomer is predominant (84TL4867; 86TL431). Comins and Abdullah have reported that a 4-stannyl-substituted pyridinium salt is a better substrate for synthesizing 2-substituted pyridinium derivatives (82JOC4315). Other groups have been used by Kawanishi and co-workers (85JOC287; 86TL211), Webb (85TL3191), and Courtois *et al.* (85TL1027). Among those groups, allyl tributyltin is quite useful for introducing an alkyl group onto the 2-position of the pyridine ring, while obtaining both high regioselectivities and high yields as shown in Table IX and Scheme 18.

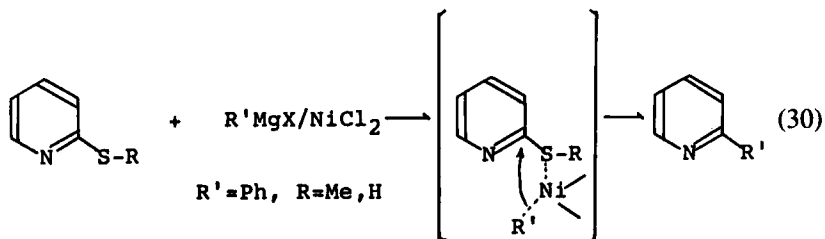
TABLE IX
REGIOSELECTIVE REACTIONS OF *N*-PYRIDINIUM SALTS WITH
ORGANOMETALLIC REAGENTS

					
R'	RM	Reaction	Conditions	Yield	Ratio
		Solvent	Temp.(°C)	(%)	α:γ
CO ₂ Et	CH ₂ =CHCH ₂ Al ₂ nBr	Et ₂ O	-78	80	98:2
CO ₂ Et	(CH ₂ =CHCH ₂) ₂ CuLi	THF	-78	72	94:6
CO ₂ Et	CH ₂ =CHCH ₂ MgBr	Et ₂ O	-78	80	96:4
CO ₂ Et	CH ₂ =CHCH ₂ ZnBr	THF	-78	60	94:6
CO ₂ Et	CH ₂ CH=CHCH ₂ Al ₂ nBr	THF	-78	60	50:50
CO ₂ Et	CH ₂ =C=CHAl ₂ nBr	THF	-78	60	58:42
CO ₂ Et	CH ₃ C=CCH ₂ Al ₂ nBr	THF	-78	50	15:85
CO ₂ Ph	EtO(CH ₂) ₄ MgCl	THF	-20	85	only
CO ₂ Me	EtMgBr	THF	-20	73	64:36
CO ₂ Me	PhMgCl	THF	-20	80	93:7
CO ₂ Me	<i>i</i> -PrMgCl	THF	-20	82	41:59
CO ₂ Me	 MgBr	THF	0	56	79:21
CO ₂ Me	 SiMe ₃	CH ₂ Cl ₂	0	0	---
CO ₂ Me	 SnBu ₃	CH ₂ Cl ₂	0	87	94:6
CO ₂ Me	PhCH ₂ SnMe ₃	CH ₂ Cl ₂	0	68	0:100
CO ₂ CH ₂ CCl ₃	PhCH ₂ SnMe ₃	CH ₂ Cl ₂	0	100	0:100

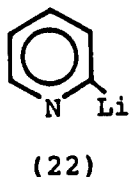


SCHEME 18

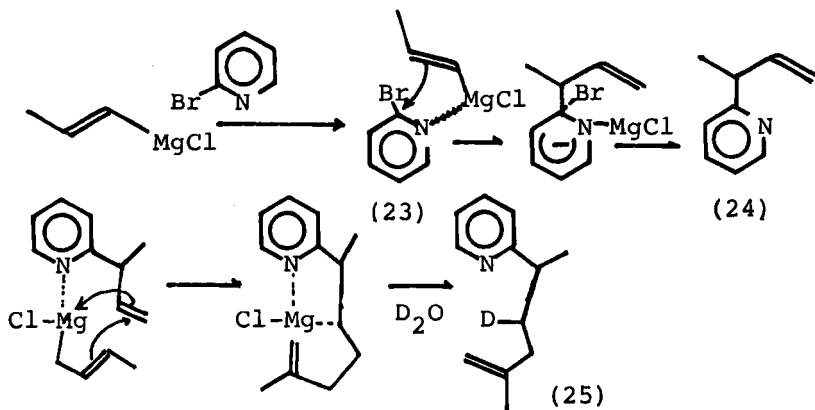
Takei *et al.* (79CL1447), Wenkert *et al.* (85JOC1125), and Potts *et al.* (87JA3961) have reported useful procedures for introducing carbon-centered groups into the pyridine ring. Their method is to treat the appropriate pyridyl sulfides with Grignard reagents in the presence of $\text{NiCl}_2(\text{dppe})$ [$\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2$] which acts as the catalyst. Although the mechanism for this reaction has not been well elucidated, the sulfide initially forms a nickel-sulfide complex which then reacts with the Grignard reagent to give the ipsosubstitution products in high yields [reaction (30)].



According to recent MO calculations on the stability of the lithium salts of pyridine, 2-lithiopyridine is energetically more stable than the 3- and 4-derivatives, because it forms the lithio-bridged structure **22**



(87BCJ3785). Furthermore, 2-bromopyridine and related azaaromatics have been reported to react with allyl Grignard reagents to initially form complex **23** between the pyridyl nitrogen atom and the Grignard reagent.

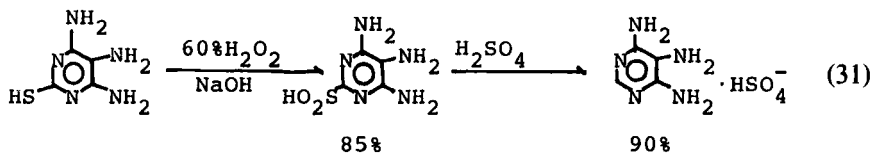


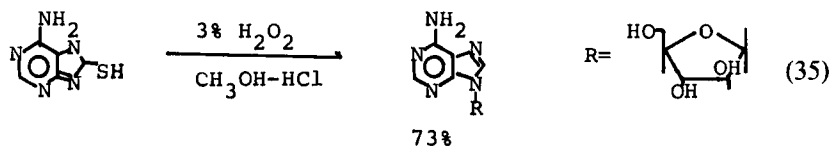
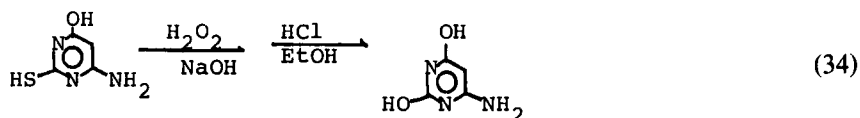
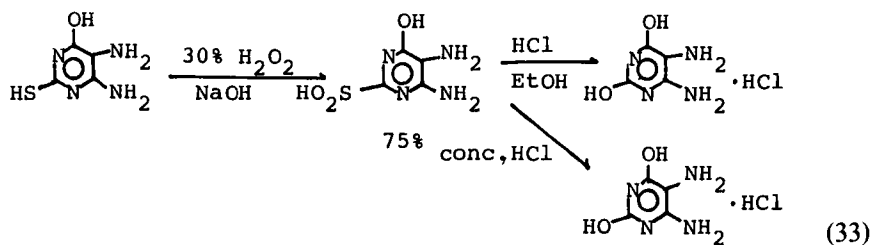
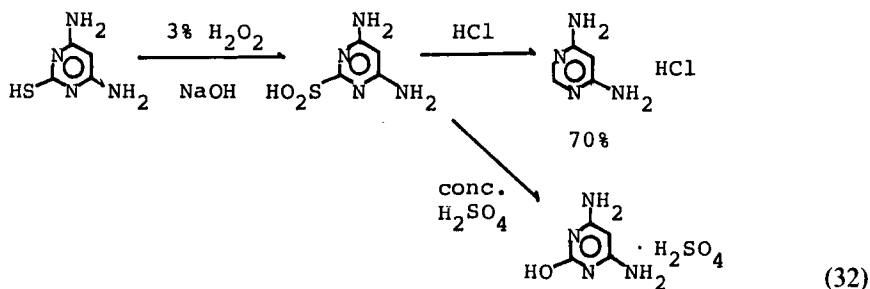
SCHEME 19

This reaction is followed by allylic rearrangement to give 2-allylpyridine **24**. This monosubstituted complex **24** reacts further with another allylic Grignard reagent to give the final coupling product **25** (81JOC4494) (see Scheme 19). All these results suggest that complex formation between the nitrogen atom in the pyridine ring and the organometallic reagent plays an important role.

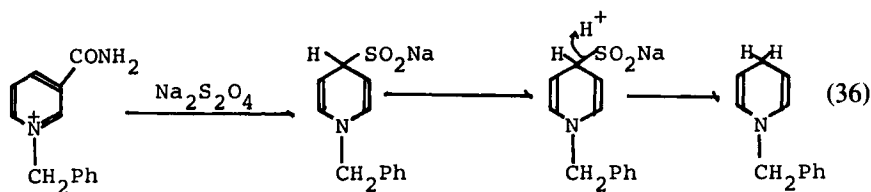
C. MISCELLANEOUS DESULFINATIONS

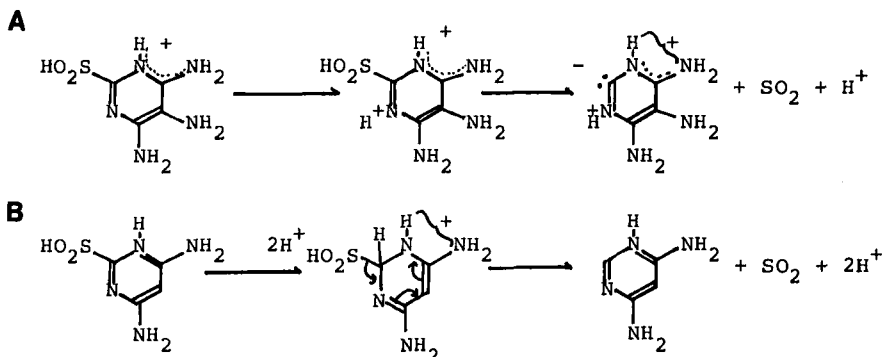
Besides the results described in Section II, B, various other hetero-aromatic compounds bearing sulfur functional groups undergo ipso substitution reactions. For example, 2-mercaptopyrimidine derivatives can be readily prepared by condensing thiourea with α -dicarbonyl compounds. The 2-mercapto group can be converted to the corresponding sulfinic acid upon oxidation, and the sulfinic acid thus obtained can readily be desulfinated when treated with mineral acids such as sulfuric and hydrochloric acids (562CS4106; 60JOC148; 72T3695). A few examples are shown in reactions (31)–(35). The desulfination proceeds either via an "acid-





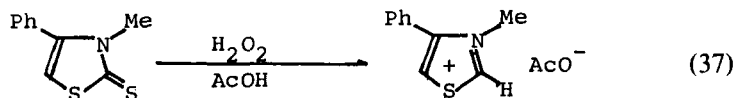
catalyzed zwitterionic route," as suggested by Evans *et al.* (56JCS4106), or by an S_E process as shown in Scheme 20. The reduction of *N*-benzyl nicotinamide with $\text{Na}_2\text{S}_2\text{O}_4$ is considered to proceed via formation of the sulfinate adduct, which then undergoes desulfination to afford the dihydronicotinamide as shown in reaction (36) (72CRV1). The thiazoline-2-thione



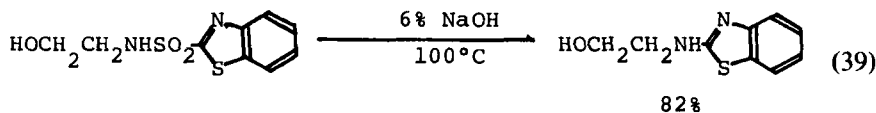
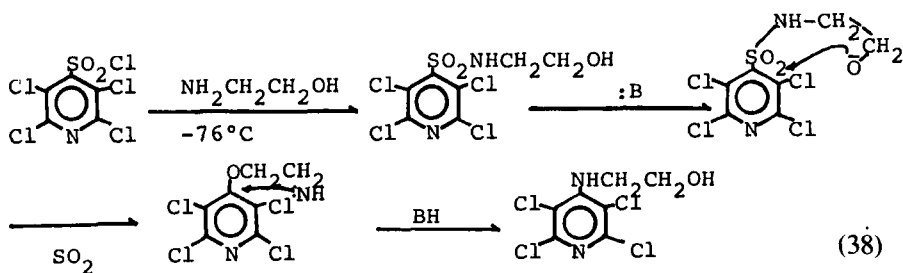


SCHEME 20. Desulfination reactions. (A) acid-catalyzed zwitterion mechanism, (B) S_E2 mechanism.

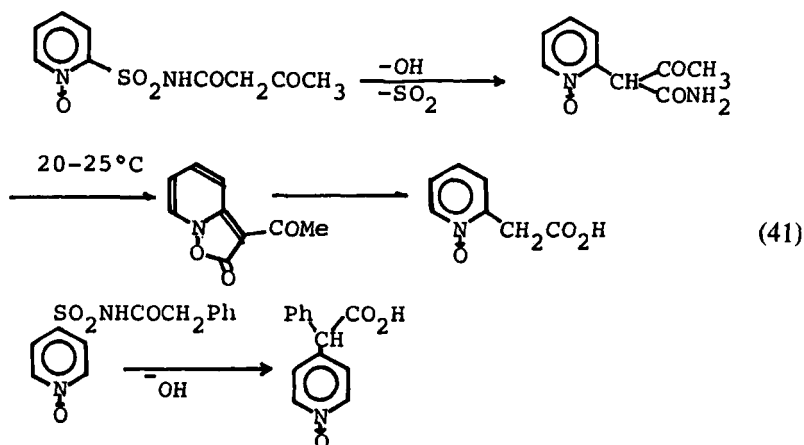
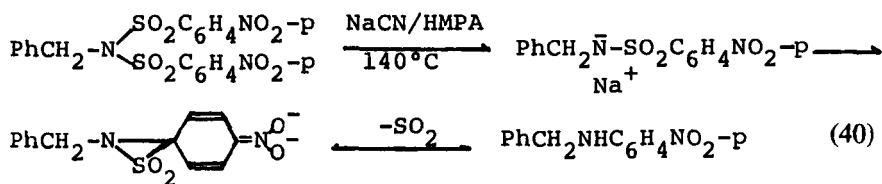
in reaction (37) is known to convert to the unstable sulfinic acid



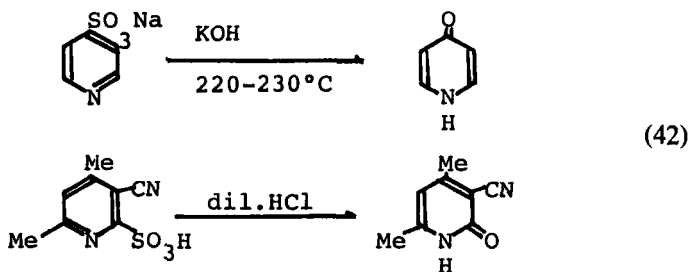
(49USP2509453-4) prior to losing SO_2 , to give the thiazole (49JOC1111; 71CPB2222; 76SZP196649). In a desulfinative double Smiles rearrangement [73JCS(p1)2971], the intermediate sulfonamide can be obtained under mild conditions [reaction (38)]. A similar Smiles-type rearrangement was also noticed in reaction (39) (68AG284; 76YZ589; 76YZ600).



The following reaction is interesting in that the Ramberg-Bäcklund rearrangement is considered to be involved in the desulfinylation process (79HCA494) [reaction (40)]. An interesting example of the intramolecular desulfonylation via the Smiles rearrangement is shown in reaction (41). (55CPB38; 64CPB588).



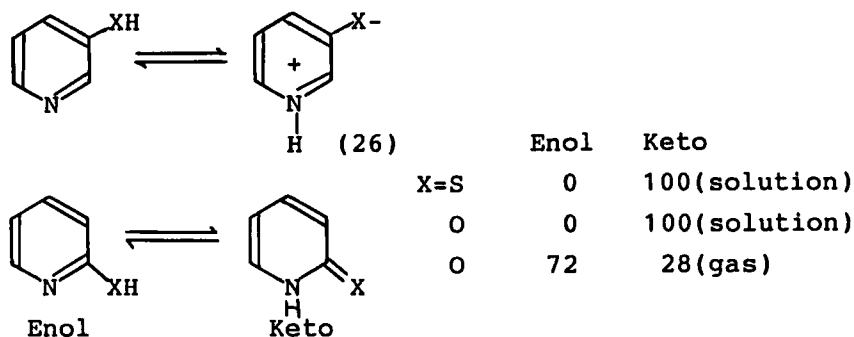
All these desulfinations have been widely used in preparing drugs. The sulfonic acid group at either the 2- or 4-position of the pyridine ring has been removed under drastic reaction conditions such as alkaline fusion or fusion with cyanide salt above 200°C . The sulfonic acid group can also be removed by treating it with acidic media, e.g., aqueous HCl (58RTC963; 60CB1590) [reaction (42)].



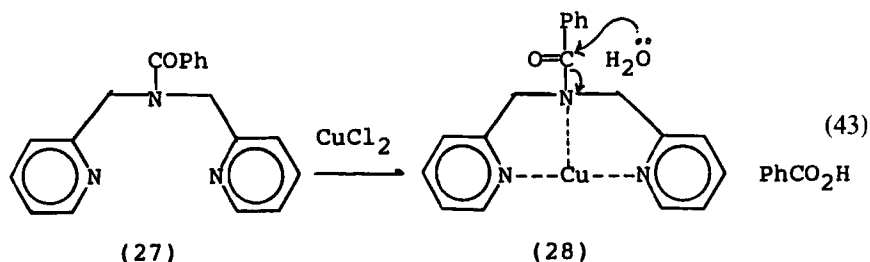
IV. Thione–Thiol Tautomerism and Its Application to Organic Synthesis

Generally, 2- and 4-hydroxyl or thiol-substituted pyridines exist as tautomeric mixtures of keto and enol forms in aqueous solution [63AHC311; 70JCS(D)1270; 76AHC1, 76JA171; 79JA3017, 79MI2; 81JA3233; 82JA612]. In nonpolar solvents particularly, the keto form is thermodynamically favored over the enol form (Scheme 21). However, in gas phase, the enol structure is known to be preferential. Evidence of the formation of keto- and enol-tautomeric structures in 2- and 4-substituted pyridines and related azaheteroaromatic compounds is found in spectroscopic studies, the results of which have been reviewed by Molina and co-workers (85TL469). On the other hand, the 3-isomer of hydroxyl or mercaptopyridine derivatives is known to exist as a zwitterion (**26**) as shown in Scheme 21. Azaaromatic groups are well known to form complexes with various metallic salts including not only alkalines and alkaline earth metals, but also transition metals. Thus, azaaromatic compounds and their derivatives bearing functional groups are widely used as ligands for metallic salts that play important roles in phase-transfer catalyses, or as enzymic model compounds. One such salt is shown in reaction (43), in which the acid amide (**27**) was reported to undergo facile hydrolysis in aqueous MeOH in the presence of CuCl_2 . The three nitrogen atoms of the two pyridine rings together with the amide group form a copper complex (**28**) which activates the carbonyl carbon atom [70JCS(D)1270]. Many examples of the activation of esters or amides by forming a complex with a metal cation between the nitrogen atom and the acyl groups in the azaaromatic compounds have been reported. (79JA3017; 81JA3233; 82JA612).

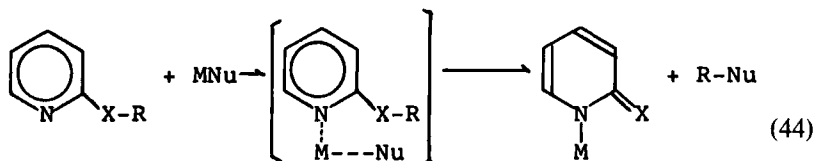
As shown in the previous sections, pyridine and related azaaromatic compounds possess a strong electron-withdrawing property equivalent to the *p*-nitrophenyl group and hence serve as good leaving groups. The facile



SCHEME 21. Keto–enol tautomerism.



complexation with heavy metals usually further enhances the leaving ability of the azaaromatic group. Therefore, if the hydroxyl or thiol derivatives of pyridine, i.e., ethers, esters, or thiol esters are treated with nucleophiles, the initial formation of a complex between a metallic cation and the nitrogen atom activates the pyridyl group for subsequent nucleophilic attack on the carbon atom attached to the oxygen or the sulfur atom. This results in the facile substitution shown in reaction (44). Usually,

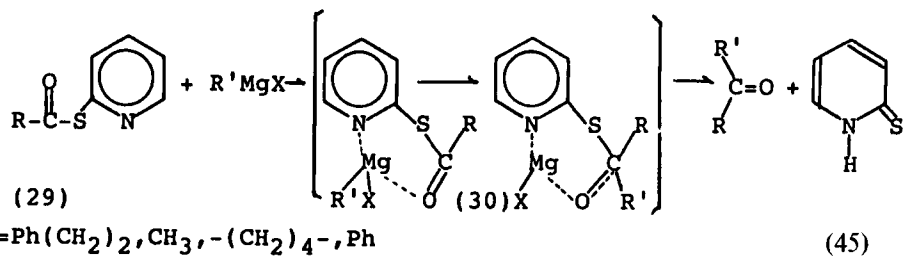


$X=O, S$ $M: Li, Na, K$

$R=Alkyl, Acyl, Anhydride$

pyridone or thiopyridone is the major component in keto-enol tautomerism, and thus pyridone or thiopyridone becomes a good leaving group for facilitating substitution on the carbon atom adjacent to the oxygen or the sulfur atoms which are attached to the azaaromatic compounds.

The compounds bearing an acylthio group (29) are called "active esters or thioesters" and are used as convenient reagents for organic synthesis (62LA90; 72CL793). Several such reagents have been used for the synthesis of ketones, esters, and amides. Reaction (45) depicts an elegant method



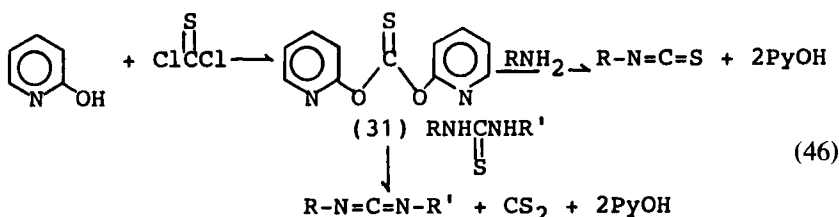
$R=Ph(CH_2)_2, CH_3, -(CH_2)_4-, Ph$

$R'=Ph, n-C_5H_{11}, n-C_4H_9, cyclo-Hex$

Yield of ketone= 92-98%

for preparing ketones by treating 2-pyridyl thioesters with Grignard reagents. In this reaction, formation of *t*-alcohols, which are generally obtained in the reactions of esters with Grignard reagents, can be avoided since the magnesium ion may chelate both the carbonyl oxygen atom and the pyridyl nitrogen atom to form complex **30**, thus highly activating the carbonyl group of the esters. The Grignard reagents attack **30** preferentially on the ester carbonyl group [73JA4763; 74BCJ1777; 79AG(E)707, 79CL1483; 80CL51, 80CL905].

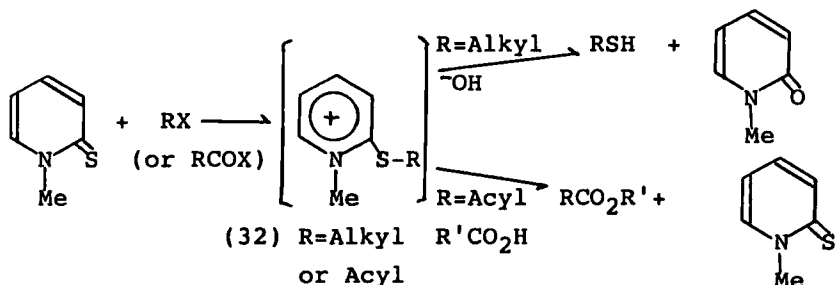
Di-2-pyridyl sulfite and thionocarbonate are prepared by treating 2-pyridyl alcohol with either SOCl_2 or thiophosgene in the presence of triethylamine. Newly prepared reagents, 2,2'-bispyridylmonothiosulfites (**31**), can be used as the starting material for a number of derivatives such as *N*-sulfinylamines, nitriles, isothiocyanates, and carbodiimides. Typical examples of these reactions are shown in reaction (46) (84TL4943;



$\text{R, R}' = \text{PhCH}_2, \text{Ph}, p\text{-Tol}, \alpha\text{-Nph}, n\text{-Bu}, \text{CH}_2=\text{CH}_2\text{CH}_2, t\text{-Bu},$

Yield: 85-95%

85TL1661; 86TL1925). The thiocarbonyl group in *N*-alkyl-2-(¹*H*)-thiopyridine is highly nucleophilic and hence reacts with alkyl halides or acyl chlorides to afford the quite reactive *N*-methyl-2-alkyl- or *N*-methyl-2-acylthiopyridinium salts (**32**). These salts are more reactive than the starting pyridine derivatives and readily undergo hydrolysis upon treatment with aqueous alkali or carboxylic acid to give the corresponding thiols or acid anhydrides in high yields [reaction (47)] (77JOC2180; 79CC179).

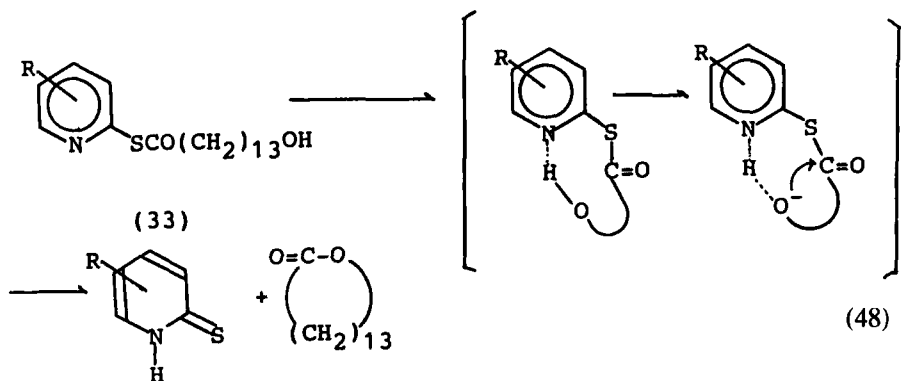


$\text{R} = \text{PhCH}_2, \text{Ph}(\text{CH}_2)_2, \text{cyclo-Hex}, \text{ClCHCOPh}$

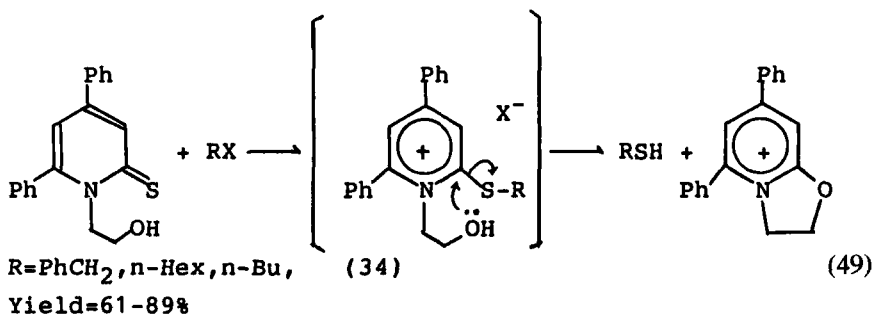
$\text{R}' = \text{Ph}(\text{CH}_2)_2, \text{PhCOCH}_2, \text{Me}_2\text{CH}, p\text{-Tol}$

(47)

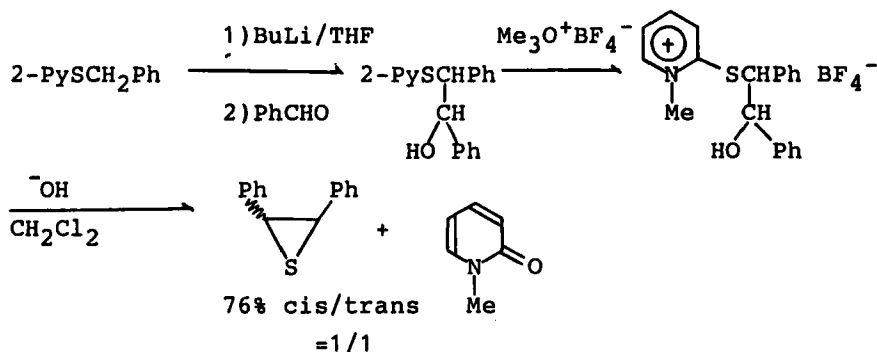
Various other condensation reactions using similarly active esters of pyridine derivatives have been reported. 2,2'-Bipyridyl-6-yl carboxylates undergo facile alcoholysis in the presence of CsF as the catalyst to give the corresponding esters. The reaction is especially applied to the selective acylation of a primary alcohol group in diols (81CL531). Intramolecular cyclization of pyridyl thioesters bearing a hydroxyl group (33) attached at an appropriate end of the long alkyl chain has been performed. In this reaction the pyridyl nitrogen atom serves as an intramolecular base which abstracts a proton from the alcohol, thus activating both the pyridyl and thiocarbonyl groups and eventually resulting in lactone formation [reaction (48)], (81TL275).



Katritzky *et al.* reported that alkyl halides convert to thiols in one pot when treated with a thiopyridine, which initially transforms to the pyridinium salt (34). Intramolecular ipso substitution takes place in the salt (34) by the remote hydroxyl group to afford the corresponding thiols shown in reaction (49) (85TL469). Thus, pyridinium sulfides readily undergo both



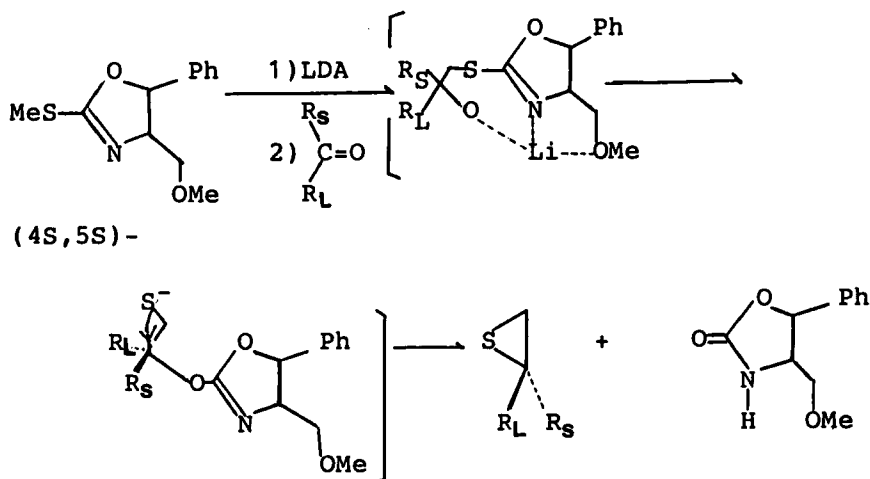
inter- and intramolecular nucleophilic attack by alkoxide anions as described previously. However the α -carbon atom of the pyridylthio group can give a carbanion when treated with a strong base. This reaction can be



SCHEME 22. Preparation of episulfide.

used for the elegant one-pot synthesis of episulfides. A similarly convenient process for these thiirane derivatives is shown in Scheme 22 (72CPB2067; 75TL2865; 77S884; 79G703).

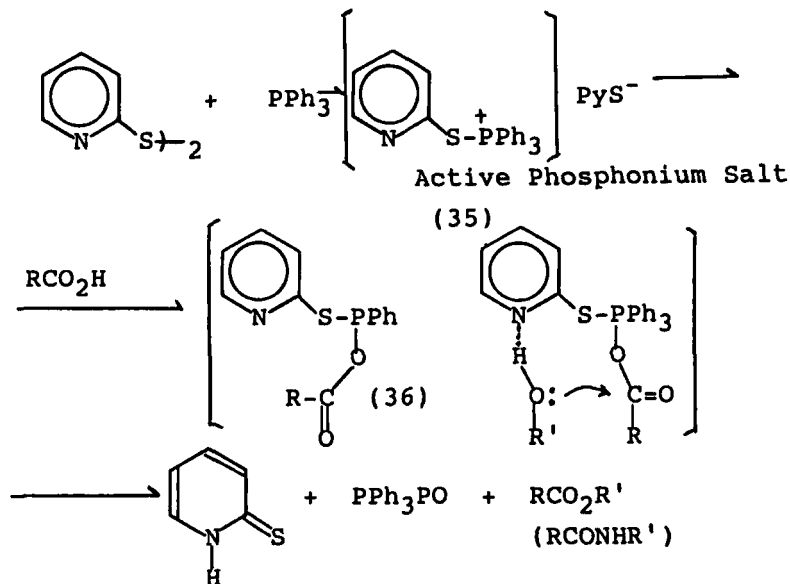
Meyers and Ford (76JOC1735), and Hirai *et al.* (72CPB206) have used 2-(alkylthio)-2-oxazolines or thiazolines to prepare the corresponding thiiranes upon treatment with bases and subsequently with carbonyl compounds. The reactions of 2-pyridyl sulfides are expected to proceed similarly as shown in Scheme 22, since the oxazoline ring is a good leaving group in the intramolecular substitution reaction. When optically active oxazolines are used, asymmetric induction takes place to afford the optically active thiiranes in 19–32% enantiomeric excess (ee). The process is shown in Scheme 23.



SCHEME 23. Preparation of optically active episulfide.

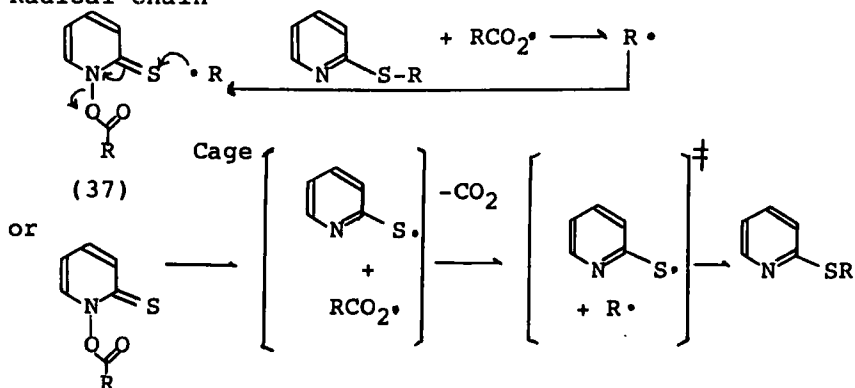
Another versatile condensing agent for the formation of esters or acid amides is a combination of pyridyl disulfide and triphenyl phosphine (70TL1901; 74MI2). Similarly, numerous condensing systems have been invested and used for organic syntheses [74JA5614; 75JA3515; 76TL3409; 79AG(E)2309]. In this reaction, the reactive species is definitely phosphonium salt (35) which reacts with a carboxylic acid to form the incipient phosphorane (36) as the intermediate. The acyl group on the phosphoranes (36) can be attacked readily by numerous alcohols and amines to give the final esters and amides, respectively. The system can be applied in the synthesis of peptides as shown in Scheme 24.

Recently, Barton *et al.* have extensively studied the pyrolysis and photolysis of thiohydroxamic acids (37) which are prepared from 1-hydroxy-2-thiopyridone and acyl chlorides. In the pyrolysis, alkyl radicals are generated via the initial formation of acyl radicals produced by the homolysis of the *N*-acyl bond. The alkyl radicals thus formed add to the sulfur atom in the 2-thiopyridones to further initiate the homolytic fission between the nitrogen and the acyl oxygen bond in the molecules (37). Propagation of the free-radical chain reaction gives the alkyl halides by abstraction of the halogen atom from such solvents as CCl_4 and CBrCl_3 . A radical initiator, such as azobisisobutyronitrile, is used for the reaction. This reaction is considered to be a modification of the Hunsdiecker reaction without using



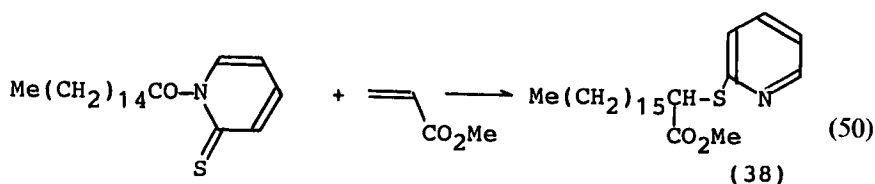
SCHEME 24. Reaction of active ester.

Radical chain

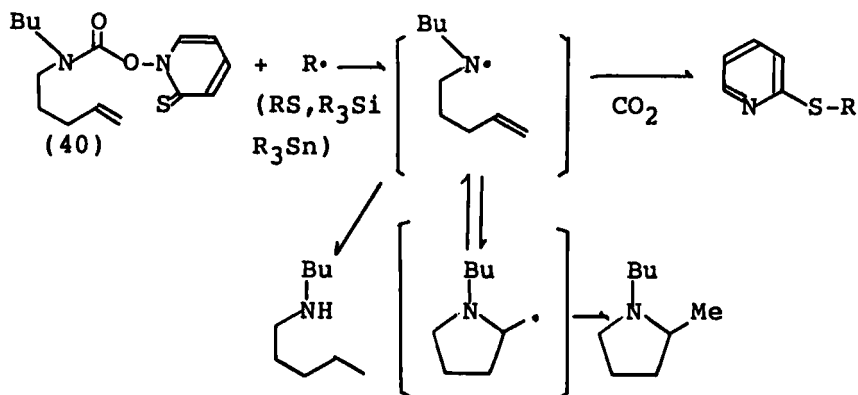


SCHEME 25. Radical chain mechanism.

conventional heavy metal salts such as silver or mercury salts, but is mediated by thiopyridone (83CC939, 83TL4979, 83TL5889). Various oxygen esters of prepared thiohydroxamic acids readily undergo thermal radical fission followed by the subsequent migration of the R group in a cage from the carbon to the sulfur atom as shown in Scheme 25. Free radical chain processes are the exclusive processes in the photolysis of these hydroxamic acids and are predominate in the pyrolysis. The alkyl radicals thus generated undergo a number of interesting reactions to afford, for example, the corresponding alkane, when the reaction is carried out in the presence of *t*-BuSH. The Hunsdiecker products and also the addition products (38) from the electrophilic olefins are also formed. Product 38 is obtained via an initial radical intermediate which subsequently migrates to the thione sulfur atom as shown in reaction (50) (84TL1055). This process

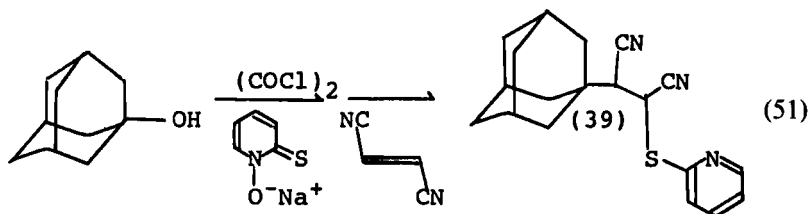


can be used to generate prim-, sec-, and tert-radicals by selecting the appropriate carboxylic acids or their derivatives (84TL5777). A convenient procedure for generating alkyl radicals starting from tert-alcohols in one pot has also been reported. For example, a tert-alcohol such as 1-admantanol is initially converted to the hemioxalate, then to the hydroxamate. The *tert*-alkyl radical is similarly generated upon pyrolysis as in the



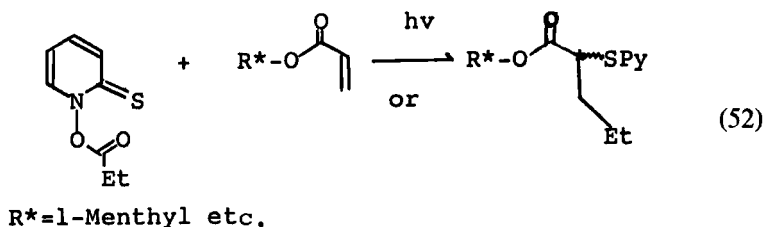
SCHEME 26. Generation of imminium radical.

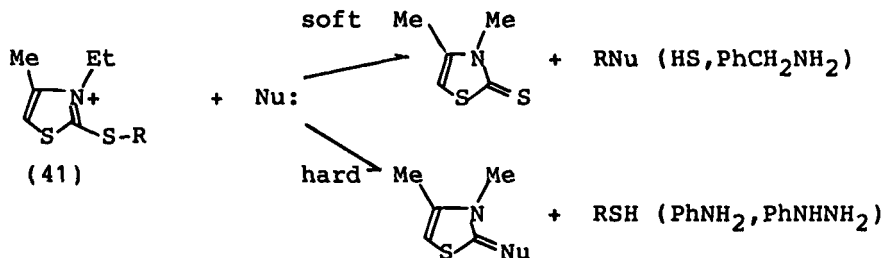
other alcohols. The *tert*-alkyl radicals are found to add to common olefins; thus the quaternary carbon compounds (39) are obtained as shown in reaction (51). (85TL757).



A similar procedure has successfully generated aminyl radicals by treating the *N*-carbamates of *N*-hydroxyl-2-thiopyridones (40) with radical initiators such as $RS\cdot$ and $R_3Si\cdot$. The aminyl radical generated abstracts a proton or adds intramolecularly to the double bond to result in the cyclization products shown in Scheme 26 (87JA3163).

Asymmetric induction using an optically active acrylate ester with *O*-ethylthiohydroxamate has also been reported (87TL4205). [See reaction (52).] A review on the photolysis and thermolysis of *O*-hydroxamic thio-





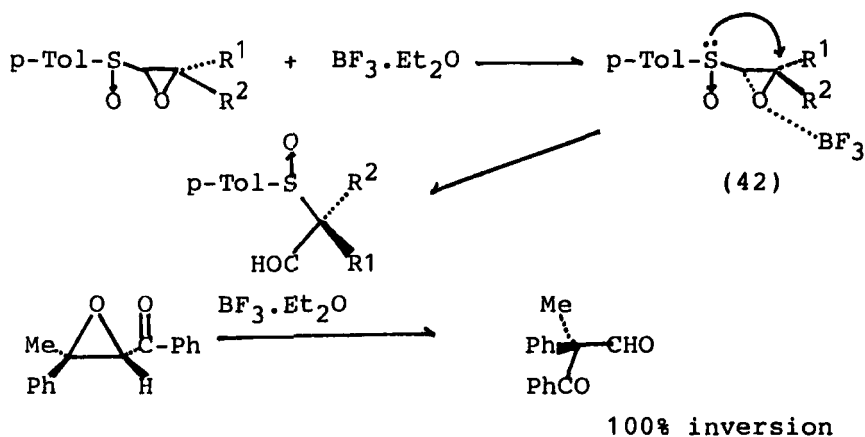
SCHEME 27. Reaction modes.

acid was presented by Crich (87MI3). There are a few discussions about the site of nucleophilic attack on the azaaromatic compounds bearing sulfur functional groups. In the reactions of thiazolinium salts (41), hard nucleophiles such as aniline and phenylhydrazine are believed to attack the ring carbon atom bearing the sulfinyl group, while soft nucleophiles such as thiolate and benzylamine attack the alkyl carbon atom of the sulfinyl group to give the corresponding substituted products shown in Scheme 27 [72BCJ1797; 73JA2749; 74JA296, 74JCS(P1)2610].

V. Miscellaneous Reactions

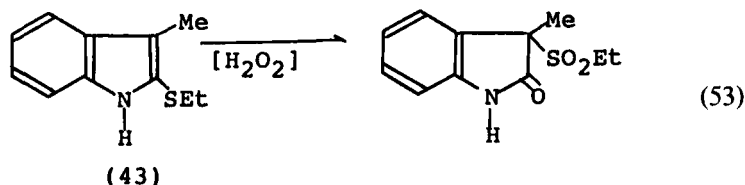
A. INTRAMOLECULAR REARRANGEMENT OF SULFUR FUNCTIONAL GROUPS

Sulfoxides bearing an epoxide ring directly attached to the sulfinyl sulfur atom have been found to undergo concomitant ring opening and migration of the sulfinyl group when the starting sulfoxides are treated with suitable Lewis acids such as BF_3 -etherate (70TL2369, 70TL2373). This interesting rearrangement is considered to proceed via the initial interaction of BF_3 with the oxygen atom of the epoxides to give the carbon cation-like intermediate 42. Intermediate 42 is then attacked by the sulfinyl sulfur atom from the back side of the carbon atom (Scheme 28). Like the sulfinyl moiety, other functional groups such as the carbonyl and carboxyl groups which are vicinally attached to the epoxide ring, have been observed migrating concertedly to the adjacent carbon atom, since the stereochemistry of the migration at the migration terminus is nearly a complete inversion process (85TL6039). Furthermore, 1,2-migration of the sulfur functional group has been reported in the indole and pyrrole ring systems. The functional group attached originally at the 2-position in the ring migrates to the 3-position. Hino *et al.* have demonstrated that the 2-ethyl-



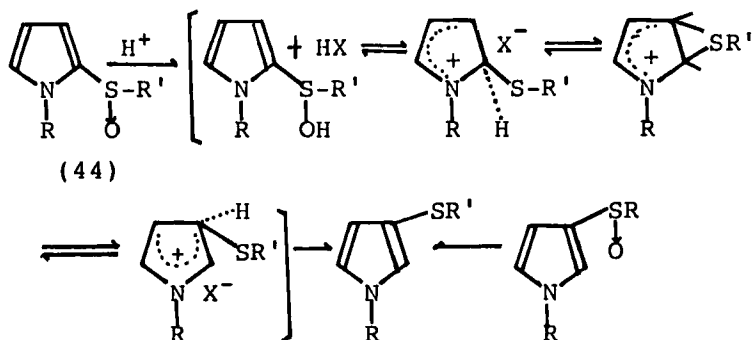
SCHEME 28. Rearrangement of epoxides.

sulfenyl group in 3-methylindole derivative (43) migrates to the 3-position when the sulfide is treated with a 3M excess of hydrogen peroxide to eventually give 3-methyl-3-ethylsulfonylindolinon [reaction (53)]. One



equivalent of the oxidant results in the formation of the corresponding sulfoxide which remains at the 2-position. The reaction can be explained in terms of the initial formation of the reactive epoxide ring between the 2,3-positions of the pyrrole ring (72CC473). Other examples of the rearrangements of electron-withdrawing functional groups in the indole ring have been summarized by Acheson (71ACR177).

The sulfinyl or the sulfenyl group in 2-substituted pyrroles (44) has been observed to rearrange to the 3-position in the ring when treated with acyl halide in acidic media or under Pummerer-like reaction conditions (82JOC3668; 85TL2831). The reaction is considered to proceed via the initial protonation at the sulfinyl oxygen atom to facilitate the elimination of the hydroxyl group or by protonation of the 2-position of the pyrrole ring. Subsequently the sulfinyl or the sulfenyl group migrates intramolecularly to the 3-position in the pyrrole, thermodynamically affording the more stable 3-isomer (Scheme 29). This procedure provides a convenient

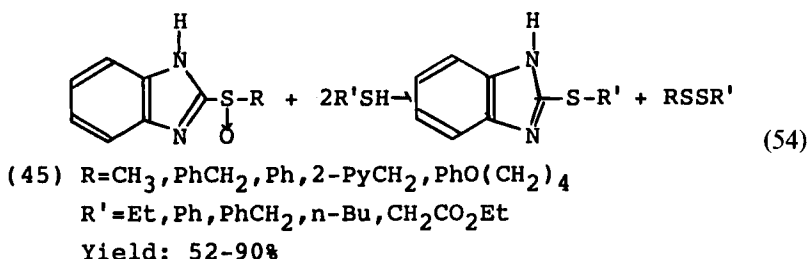


SCHEME 29. 1,2-Migration of sulfoxide.

way to introduce an appropriate electron-withdrawing functional group to the 3-position of the pyrrole.

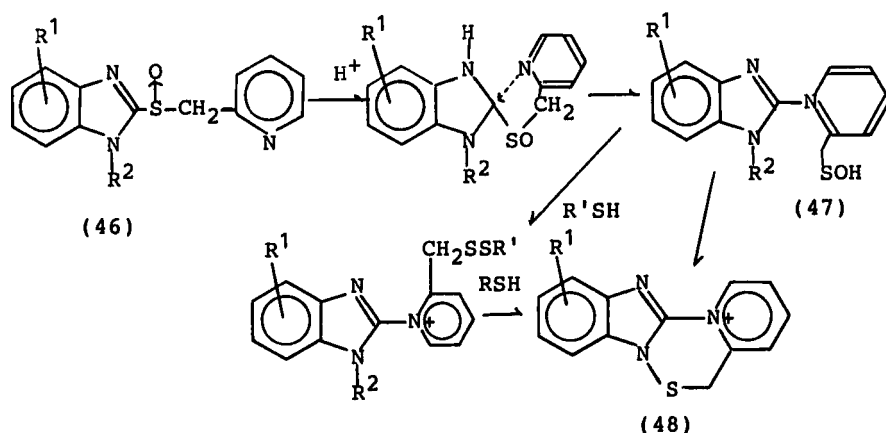
B. INTRAMOLECULAR REARRANGEMENT OF BENZIMIDAZOLE SULFOXIDES

Sulfoxides are well known to undergo facile reduction upon treatment with thiols and other acids to afford the starting sulfides and symmetrical disulfides. The mechanisms for the acid-catalyzed reduction of the sulfoxides have been extensively investigated. These reactions are used for simple preparations of symmetric disulfides (770PP63; 82MI1, p. 379). However, when 2-alkylsulfinyl- or 2-arylsulfinyl- 1,2-alkylsulfinyl-benzimidazoles (45) are treated with thiols, the unsymmetrical disulfides are obtained, instead of ordinary symmetrical disulfides together with ipsosubstitution products of the benzimidazole rings [reaction (54)]



(87JOC4620). The reaction is considered to be initiated by protonation at the nitrogen atom of the benzimidazole ring. The sulfenic acid is eliminated

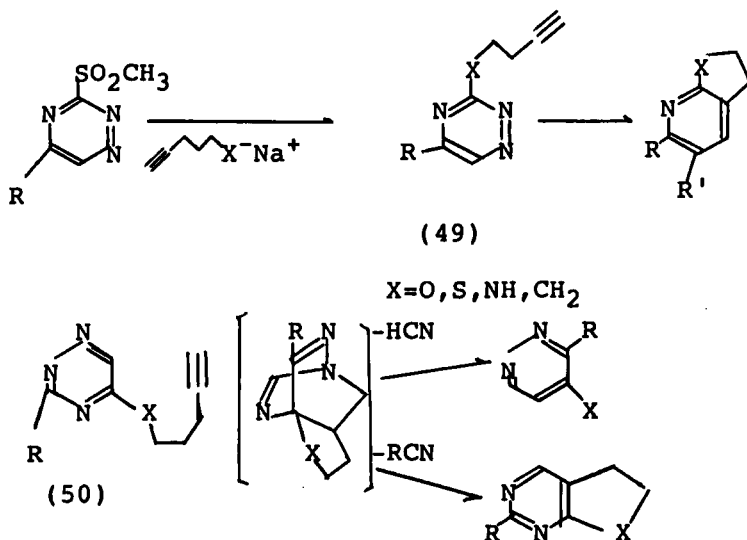
after the ipso substitution of the benzimidazole ring by the thiolate. The sulfenic acid, once formed, is highly unstable and reacts immediately with the thiols in the medium or dimerizes to the corresponding thiolsulfonates from which the unsymmetrical disulfides are prepared. Thus, by selecting a suitable combination of the ligands on the sulfoxide (45) and the thiol reducing agent, many unsymmetrically substituted disulfides can be prepared in good yields. Meanwhile, 2-benzimidazolyl 2-picolyl sulfoxides (46) show different reactivities upon treatment with thiols and strong acids such as HCl. In this reaction of the sulfoxides (46), an intramolecular rearrangement of the picolyl group was observed. The reactions have been demonstrated to proceed via the initial protonation of the imidazolyl nitrogen atom to form a carbonium ion at the 2-position; the pyridyl nitrogen atom then attacks intramolecularly to give the sulfenic acid (47) as the intermediate. The sulfenic acid (47) thus formed reacts further with other thiols to give the corresponding unsymmetrical disulfides as shown in reaction (54), or it undergoes an intramolecular condensation with the nitrogen atom of the imidazole ring to give the sulfenamide (48) (Scheme 30). The sulfoxides described here have been reported to have an effective antiulcer activity (Scheme 30) (87JOC4573). The structure of sulfenamide (48) has been determined by X-ray crystallography (86CC125). The major role of this sulfoxide *in vivo* is the inhibition of $(\text{H}^+ - \text{K}^+) \text{ATPase}$ by temporarily blocking the SH-group in this enzyme.



SCHEME 30. Acid catalyzed rearrangement of sulfoxides.

C. SULFUR AS AN AUXILLIARY IN THE DIELS–ALDER REACTION OF TRIAZINES

Sulfur-functional groups attached directly to azaaromatic compounds are readily replaced by nucleophiles to give the corresponding ipso-substitution products. Reactivity is increased by increasing the number of the nitrogen atoms in the heterocycles. In the 1,2,4-triazine ring system, ipso-substitution takes place and readily introduces many substituents on the ring. Furthermore, triazine has been found to undergo the Diels–Alder reaction with suitable dienophiles and converts to various other heterocycles—the triazines serve as dienes. By using appropriate substituents attached to the triazine ring, pyrimidines, pyridazines, or pyridines fused by other heterocycles can be obtained via the intramolecular Diels–Alder reaction. Taylor and co-workers have reported synthetic procedures for obtaining condensed azaheterocycles using triazines bearing dienophiles such as **49** and **50** at the suitable positions (85TL2415; 86TL431; 87JOC4280, 87JOC4287, 87TL379). If 2-substituted dienophiles (**49**) are used, then pyridine rings fused by heterocycles such as thiophene, furan, pyrrole, or cycloalkanes can be obtained. When the 6-substituted derivatives (**50**) are used, either pyrimidine or pyridazine ring systems are obtained. Several typical examples are summarized in Scheme 31.



SCHEME 31. Diels–Alder reaction of triazines.

VI. Conclusion

The chemistry of both organic sulfur compounds and azaaromatic compounds has been widely investigated mainly for industrial purposes for many years, and vast amounts of data have been accumulated. However, many studies lack mechanistic support.

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Diazoazoles

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I. Introduction

Diazoazoles have been known since 1892 when Thiele first prepared the diazotetrazole. After Bamberger isolated 3-diazoindazole near the end of the last century, this class of compounds received remarkable attention as testified by several reports on the synthesis and chemistry of diazoindoles and diazopyrroles in the first decade of this century. However, only since the 1950s, with the suggestion of the structure of diazocyclopentadiene

and with the improvement of techniques for isolation and purification, has the chemistry of diazoazoles received a strong impetus. Since then interest has expanded exponentially.

With the exception of Tedder's chapter in this series (67AHC1), now out of date, no attempts have been made to cover all aspects of the chemistry of diazoazoles. Some of them were treated in reviews that had as a topic the chemistry or use of heterocyclic diazo compounds as synthons for organic synthesis [76H1115; 80KGS579; 82H(19)559] or that studied the diazotization of heterocyclic amines [75CRV242; 86AHC(40)129]. Some details on the biological properties of some diazoazoles are also reported in a review on the medicinal application of azolotriazines to which diazoazoles are closely related (76MI1). The aim of this review is to cover the structural aspects, reactivity, preparations, and applications of diazoazoles. Although this class of compounds is characterized by the presence of the diazo group in the azole nucleus, their stability and reactivity widely depends on the mutual influence of the heterocycle and the diazo function. Generalization is sometimes impossible because they range from an electron-rich nucleus, such as pyrrole, to a very electron-deficient one, such as tetrazole. Nevertheless, whenever possible, we will try to elucidate the common aspects of their chemistry and reactivity or, failing this, deal with them separately.

II. Structure and Physical Properties

All the studies on the elucidation of the structure of diazoazoles lead unequivocally to a mesoionic structure in which the negative charge is localized in the azole ring. Of primary importance were ^{13}C -NMR and IR spectra, as well as X-Ray crystal diffraction data. With regard to the stability in the solid state of diazoazoles and in solution in the pH range where they are not protonated, the presence of ortho ring nitrogens destabilizes the diazo compounds.

A. CRYSTALLOGRAPHY: DIPOLE MOMENTS

X-Ray crystal diffraction studies of 4-acetyl-3-diazo-2,5-diphenylpyrrole (**1**) and of 3-diazoindazole (**2**)¹ are the only examples reported because of difficulties in obtaining suitable crystals [78AX(B)293; 88UP1] (Fig. 1).

¹ Not shown.

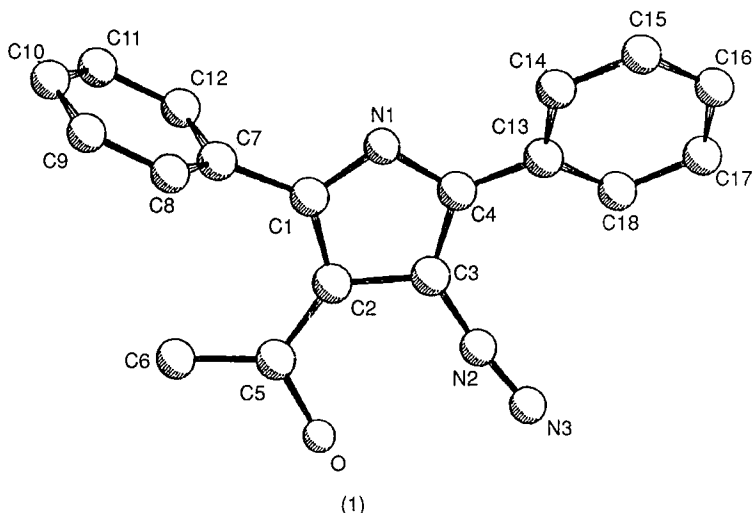
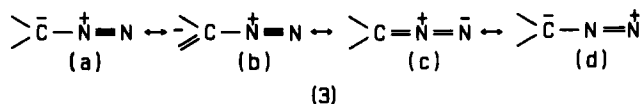


FIG. 1. Molecular structure of compound 1. The diazo group in 1 is coplanar to the pyrrole ring and the C(3)—N(2)—N(3) angle is 171(1)°.

In the diazo group of both these heterocycles, the C—N bond distances were intermediate between a single and a double bond and shorter than the corresponding average C—N bond length [1.40(2) Å] found in aromatic diazonium compounds, but they are close to the values in aliphatic diazo compounds (1.32 Å in diazomethane). The N—N distance of the diazo group in diazomethane is 1.113 Å, suggesting a “carbanionic” dipolar character due to structure **3a** rather than structure **3b** or **3c** shown in Scheme 1. The distances C(3)—N(2) [1.31(3) and 1.338 Å] and N(2)—N(3) [1.13(3) and 1.110 Å] of the diazo group found for compounds **1** and **2**, respectively, also demonstrate the carbanionic character of C(3)—N(2)—N(3) (Fig. 1). All the other bond lengths are intermediate between single and double bonds, indicating thus a substantial conjugation in the heterocycles. In compound **1**, the molecular conformation is characterized by the planarity of the pyrrole ring, whereas the adjacent phenyls are tilted 101°. With respect to the five-membered ring, the phenyl in the 5-position is tilted 83°, the other is tilted 25°. The acetyl moiety is quasi-coplanar to the pyrrole ring (the angle is 6°). In compound **2**, the indazole portion is planar and the molecules are packed in layers nearly parallel to the *ac* plane, with the interlayer separation of nearly 3.4 Å. The molecules



SCHEME 1

are held together by Van der Waals forces. The dipole moment of 2-diazo-4,5-dicyanoimidazole (**4**)² is 7.66 D (73JA2695).

B. NMR SPECTRA

¹H-NMR spectra of diazoazoles in dimethylsulfoxide-*d*₆ (DMSO-*d*₆) or CDCl₃, as expected, show no signal for an iminic proton. The addition of trifluoroacetic acid (TFA) can give rise to the diazonium species, depending on the acidity of the heterocycle. In fact, after the addition of a two-fold excess of TFA, the spectrum of 3-diazo-2,5-diphenylpyrrole showed, a signal, at 7.45 ppm, identical to that of the isolated 3-diazonium chloride in DMSO-*d*₆ (88UP2). By contrast, ¹H-NMR spectra in TFA or DMSO-*d*₆/TFA of 3-(4-diazoimidazol-5-yl)-1,2,4-triazole did not exhibit any signal for the iminic proton arising from protonation of the diazo form, suggesting that even under such conditions this compound exists in the diazo form [66CI(L)2197], or more likely, that rapid exchange takes place. In the pyrazole series, although spectra of diazo compounds in the presence of TFA are not reported, the spectrum of isolated, even if "unconventional" (see Section II,G), 5-benzoylamino-1-methyl-3-phenylpyrazole-4-diazonium bromide showed a broad signal at 9.1 ppm (84JHC957).

¹³C- and ¹⁵N-NMR spectroscopy has been used to gain information on the contributions of resonance forms of type **3** to the hybrid structure of the ground state of diazoazoles. The ¹³C chemical shifts of the ipso carbon of the diazo group in some diazoazoles are reported in Table I where those of diazomethane and of two diazocyclopentadienes are compared.

Generally, the diazo carbon is characterized by a large upfield shift, as compared with the usual range for a normal *sp*² hybridized carbon in the parent ring. These large shifts might reflect substantial contributions of resonance structures of type **3a** or **3d** [78JA4974]. This effect is not surpris-

² Not shown.

TABLE I
¹³C CHEMICAL SHIFTS OF THE IPso CARBON OF DIAZO COMPOUNDS

Compound	ppm	Solvent	Reference
Diazomethane	23.3	CDCl ₃	77OMR(9)75
	23.6	C ₆ D ₆	77OMR(9)75
Diazocyclopentadiene	72.2	C ₆ D ₆	78JA4974
1,2,3,4-tetraCN	92.6	DMSO-d ₆	78JA4974
3-Diazo-2-phenylpyrrole			
5-Ph	76.50	DMSO-d ₆	88UP2
4-CN-5-Ph	81.50	DMSO-d ₆	88UP2
4-CO ₂ Et-5-Me	80.25	DMSO-d ₆	88UP2
4-CO ₂ Et-5-Ph	79.89	DMSO-d ₆	88UP2
3-Diazoindole	60.1	CDCl ₃	77OMR(9)75
	60.3	DMSO-d ₆	75AG(E)103
1-Me	60.0	DMSO-d ₆	75CB3326
4-Diazopyrazole			
3-CO ₂ Et-5-one	67.7	CDCl ₃	78H(10)199
5-NHCOPh-1-Me-3-Ph	73.1	DMSO-d ₆	85JHC951
2-Diazo-4,5-dicyanoimidazole	112.2	DMSO-d ₆	78JA4974

ing because molecular orbital calculations showed that this carbon has a considerable electron density [77OMR(9)75]. In fact, a linear correlation exists between the calculated carbon charge densities and the diazo carbon shifts in the aliphatic series. On the other hand, a significant correlation was also found between the ipso carbon shifts of diazo compounds and the shifts of the corresponding carbons of appropriate carbanions or hydrocarbons (the C=N₂ group is replaced by CH₂) (78JA4974). This confirms that resonance forms of type **3a** contribute mainly to the hybrid structure. Moreover, because of the enhanced negative partial charge on this atom and the related long relaxation time, the diazo carbon signals have low intensities (78H(10)199). The diazo group also has a deshielding effect on the ortho carbons [77OMR(9)75; 85JHC951].

A similar upfield shift of the ipso carbon is also observed in the spectra of diazonium salts or of diazo compounds upon addition of TFA. However, the diazonium carbon is deshielded ~6–12 ppm with respect to the diazo carbon (85JHC951; 88UP2).

With regard to ¹⁵N-NMR, 2-diazo-4,5-dicyanoimidazole (**4a**) is the only diazoazole that has had its spectrum reported. The ¹⁵N chemical shifts of this compound and those of diazomethane and of two diazocyclopentadienes are reported in Table II. In all the spectra, the terminal nitrogens

are deshielded as compared to the internal ones. This is contrary to what might have been expected from the charges calculated by intermediate neglect of differential overlap (INDO) methods [77OMR(9)75], but is consistent with the presence of a lone pair on the terminal nitrogen and its absence on the internal nitrogen as implied in canonical structures such as **3c** and **3a**. In the case of compound **4a** and of tetracyanodiazocyclopentadiene, the nitrogen nuclei are shielded relative to diazomethane and are similar to those of benzene diazonium ions. Thus, these diazo compounds can be formulated as dipolar ions with a full $-^+N\equiv N$ group (78JA4974).

C. ULTRAVIOLET SPECTRA

The UV absorption maxima of diazoazoles are shown in Table III. 2-Diazopyrroles have absorption bands in the range of 345–351 nm (62JCS1638). 3-Diazopyrroles showed absorption maxima at a wide range of wavelengths (244–405 nm) depending on the nature and position of the substituents [60JCS3270; 83H(20)255]. However, the UV absorptions of 3-diazopyrroles appear at slightly longer wavelengths than the 2-diazopyrroles with analogous structural profiles (62JCS1638).

For the 3-diazoindoles, the UV maxima are ~ 350 nm. Annellation in the 4-5 and 6-7 positions shifts the maximum to higher wavelengths (63JCS4593). In diazopyrazoles, it is impossible to differentiate between the absorption maxima ranges of the 3- and 4-derivatives. Nevertheless, a hypsochromic effect was noticed in the transformation of the diazo form into the diazonium salt (61CB1036).

The 2-diazoimidazoles have absorption bands in the range 312–367 nm, and the 4-diazo isomers have absorption bands in the range 308–314 nm.

TABLE II
 ^{15}N CHEMICAL SHIFTS (PPM) OF DIAZO COMPOUNDS

Compound	N-1 ^a	N-2 ^a	Solvent	Reference
Diazomethane	90.0	−14.0	Et ₂ O	75JCS(D)2522
Diazocyclopentadiene	106.2	−8.8	<i>n</i> -pentane	78JA4974
1,2,3,4-tetraCN	147.1	41.6	DMSO- <i>d</i> ₆	78JA4974
2-Diazoimidazole				
4,5-diCN	146.0 ^b	59.4 ^b	DMSO- <i>d</i> ₆	78JA4974

^a Upfield from external 1M H¹⁵NO₃ in D₂O.

^b Ring and CN nitrogens at 82.7 and 108.0 ppm, respectively.

TABLE III
ULTRAVIOLET ABSORPTION MAXIMA OF DIAZOZOLES

Compound	nm	ϵ (10^{-3}) ^a	Solvent ^b	Reference
2-Diazopyrrole				
4-Ac-5-Me-3-Ph	351	5.7	a	62JCS1638
2,4-diPh	345	9.9	a	62JCS1638
3-Diazopyrrole				
4-Ac-2,5-diPh	250	15.09	a	83H(20)255
4-Ac-2-Me-5-Ph	244	12.08	a	83H(20)255
2,4-diMe-5-CO ₂ Et	333	3.6	a	60JCS3270
2,5-diPh	387	5.0	a	60JCS3270
2,5-diPh-4-NO ₂	399	10.0	a	60JCS3270
5-Me-2-Ph	360	10.1	a	60JCS3270
2,4,5-triPh	405	13.0	a	60JCS3270
3-Diazoindole				
1-Me-2-one	301	9.6	a	64JOC3577
5-OMe-2-(Ph-4-OMe)	346	4.0	a	63JCS4593
2-Ph	350	11.6	a	63JCS4593
2-(Ph-4-OMe)	347	9.3	a	63JCS4593
2-Ph-4-5 benzo	359	6.0	a	63JCS4593
2-Ph-6-7 benzo	368	7.7	a	63JCS4593
3-Diazopyrazole	268	e	b	61CB1036
4-CONH ₂ (pH = 1)	256	6.0	g	68JPS1044
4-CONH ₂ (pH = 11)	311	5.5	g	68JPS1044
5-COPh-4-Ph	272	22.38	c	60CI(L)659
4-Diazopyrazole				
3-CN-5-Me	283	e	d	81JCS(P1)2374
3-COPh-5-Ph	352	9.33	c	60CI(L)659
3,5-diMe	274	6.31	d	74TL1609
3,5-diPh	354	7.3	e	63JCS4589
2-Diazoimidazole	312	e	d	74TL1609
(pH = 0)	313	22.0	f	87JMC2222
(pH = 7.15)	314	24.0	g	87JMC2222
1-CH ₂ CO ₂ H (pH = 0)	313	12.0	f	87JMC2222
1-CH ₂ CO ₂ H (pH = 7.15)	299	8.0	g	87JMC2222
4-CH ₂ CO ₂ H (pH = 0)	319	22.0	f	87JMC2222
4-CH ₂ CO ₂ H (pH = 7.15)	323	23.0	g	87JMC2222
4,5-diCN	315	22.3	e	73JA2695
4,5-diPh (pH = 1)	367	22.4	g	65AAC469
4-Diazoimidazole				
5-CN	311	4.0	d	76KGS556
5-CONH ₂ (pH = 1)	293	e	g	81JCS(P1)1433
5-CONH ₂ (pH = 2.5)	312	e	g	81JCS(P1)1433
5-CONH ₂ (pH = 7.4)	310	e	g	81JCS(P1)1433
5-CO ₂ Me	314	4.4	d	67JPS147
5-(triazol-3-yl) (pH = 1)	314	6.55	g	66CI(L)2197
5-(triazol-3-yl) (pH = 7)	308	6.12	g	66CI(L)2197
5-(triazol-3-yl)(pH = 13)	308	6.34	g	66CI(L)2197

(continued)

TABLE III (continued)

Compound	nm	ϵ (10^{-3}) ^a	Solvent ^b	Reference
4-Diazo-1,2,3-triazole	269	5.01	d	74TL1609
	275	e	h	83DIS(B)(43)2557
5-CN	279	e	h	83DIS(B)(43)2557
5-CO ₂ Et	279	e	h	83DIS(B)(43)2557
5-Ph	285	e	h	83DIS(B)(43)2557
3-Diazo-1,2,4-triazole	281	5.75	d	74TL1609
5-CO ₂ H	281	9.77	i	70KGS705
5-CO ₂ Me	278	11.22	j	70KGS705
5-Diazotetrazole	261	3.39	d	74TL1609

^a e, Not reported.^b a, Ethanol; b, chloroform; c, diethyl ether; d, water; e, not reported; f, 1N HCl; g, buffer; h, methanol; i, 0.8N H₂SO₄; j, 28.3% H₂SO₄.

For the 4-diazo derivatives in which an intramolecular cyclization with the substituent in the 5-position is possible, the truly diazo form exists only in the pH range of 2.5–7.5 [66CI(L)2197; 81JCS(P1)1433]. At higher pH values, only the maxima of the cyclic products can be observed, whereas at pH < 2.5, the majority species are the protonated diazonium salts. In the 2-diazoimidazole series, however, no shift of the maximum wavelength is observed upon protonation (74TL1609), which is at variance with reports for 4-diazoimidazoles and the other diazoheterocycles (87JMC2222).

The UV spectra of 3-diazo-1,2,4-triazoles and of 4-diazo-1,2,3-triazoles have similar absorption maxima in the range of 269–285 nm. The protonation of these derivatives causes an hypsochromic shift of ~20–30 nm (70KGS705; 74TL1609). The 5-diazotetrazole shows ultraviolet maximum at 261 nm that is shifted to 235 nm upon protonation.

D. INFRARED SPECTRA

Infrared spectroscopy is the only method that gives direct, diagnostic information about the presence of a diazo group in diazoazoles. The aromatic character common to the diazoazoles and diazocyclopentadiene and the importance of the contributions of the different mesomeric forms to the resonance hybrids in the ground state are reflected in the position of the bands associated with the diazo group in the infrared spectra (Table IV).

The IR spectra of 2-diazopyrroles have very strong absorption bands in the range of 2138–2172 cm⁻¹, which are at higher frequencies than those

TABLE IV
N₂ STRETCHING BANDS OF DIAZOAZOLES AND AZOLE DIAZONIUM SALTS

Compound	cm ⁻¹	Solvent	Reference
2-Diazopyrrole			
4-Ac-5-Me-3-Ph	2146	KBr	62JCS1638
2,4-diPh	2138	KBr	62JCS1638
2,4-diPh-4-NO ₂	2172	KBr	62JCS1638
3-Diazopyrrole			
4-Ac-2,5-diPh	2130	Nujol	83H(20)255
4-Ac-2-Me-5-Ph	2120	Nujol	83H(20)255
4-Ac-5-Me-2-(4-MeOPh)	2120	Nujol	84H(22)2269
1-CH ₂ Ph-4-NHCONH ₂ -2-one	2110	KBr	74LA1550
1-C ₄ H ₉ -4-NHCONH ₂ -2-one	2105	KBr	74LA1550
4-CO ₂ Et-2-(MeOPh)-5-Me	2120	Nujol	84H(22)2269
2,4-diMe-5-CO ₂ Et	2155	KBr	60JCS3270
2,5-diPh ^a	2100	KBr	84JOC62
2,5-diPh'HCl ^a	2200	CHBr ₃	88UP2
2,5-diPh-4-CN	2120	Nujol	83H(20)829
2,5-diPh-4-CO ₂ Et	2130	Nujol	83H(20)829
2,5-diPh-4-NO ₂	2150	KBr	60JCS3270
5-Me-2-Ph	2062	Nujol	60JCS3270
2,4,5-triPh	2088	KBr	60JCS3270
3-Diazoindole			
1-H-2-one ^b	2109	KBr	64JOC3577
	2092	DCM	64JOC3577
1-Me-2-one ^c	2123	KBr	64JOC3577
5-OMe-2-(Ph-4-OMe)	2100	KBr	63JCS4593
2-Ph	2120	KBr	63JCS4593
2-(Ph-4-OMe)	2085	KBr	63JCS4593
2-Ph-4-5 benzo	2085	KBr	63JCS4593
2-Ph-6-7 benzo	2100	KBr	63JCS4593
3-Diazopyrazole	2130	CHCl ₃	61CB1036
3-Diazopyrazole'HCl	2265	KBr	61CB1036
5-t-But	2190	KBr	87JOC5538
5-t-But'HBF ₄	2290	KBr	87JOC5538
5-CH ₂ Ph-4-Ph	2119	DCM	60CI(L)659
4-CONH ₂	2222	d ₋	68JPS1044
	2215	KBr	71JPS554
4-CO ₂ Et	2210	KBr	71JPS554
4-CO ₂ Me	2215	KBr	71JPS554
5-COPh-4-Ph	2137	DCM	60CI(L)659
4-Me-5-Ph	2160	KBr	83JOC2330
4-Me-5-Ph'HCl	2250	KBr	83JOC2330
5-Ph	2170	KBr	87JOC5538
5-Ph'HCl	2280	KBr	87JOC5538
4-Diazopyrazole	2175	Film	63JCS4589
3-CH ₂ Ph-5-Ph	2123	DCM	60CI(L)659
3-CN-5-Me	2170	KBr	81JCS(P1)2374
3-CONH ₂	2222	d ₋	71JMC1245

(continued)

TABLE IV (continued)

Compound	cm ⁻¹	Solvent	Reference
3-CO ₂ Et-1-Ph-2-one	2140	CHCl ₃	78H(10)199
3-COPh-5-Ph	2146	DCM	60CI(L)659
3,5-diMe	2190	^c —	61CI(L)1163
3,5-diPh	2189	KBr	63JCS4589
3-Me-5-OEt	2120	Film	78H(10)199
5-[N=C(Ph)O]-1-Me-3-Ph	2160	KBr	84JHC957
5-[N=C(Ph)O]-1-Me-3-Ph HBr	2190	KBr	84JHC957
3-Ph-2-one	2092	DCM	60CI(L)659
3-Diazoindazole	2119	^d —	74JOC1833
2-Diazoimidazole	2150	DCM	87JOC5538
	2125	CCl ₄	74MI1
4,5-diCN	2247	^d —	73JA2695
4,5-diPh	2105	^d —	65AAC469
4-Diazoimidazole	2140	DCM	87JOC5538
2-CH ₂ Ph-5-CONH ₂	2180	KBr	87JMC357
5-CN	2180	KBr	87JMC357
5-CONH ₂	2190	KBr	81JCS(P1)1433
5-CO ₂ Et	2200	^d —	72USP3654257
5-CO ₂ Me	2180	^d —	67JPS147
5-CO ₂ Oct	2190	^d —	72USP3654257
2- <i>i</i> -Pr-5-CONH ₂	2170	KBr	87JMC357
5-SO ₂ NHMe	2210	KBr	87JMC357
5-(triazol-3-yl)	2170	^d —	66CI(L)2197
5-(triazol-3-yl)CF ₃ CO ₂ H	2235	TFA	66CI(L)2197
4-Diazo-1,2,3-triazole	2160	DCM	83DIS(B)(43)2557
5-CN	2200	DCM	83DIS(B)(43)2557
5-CONH ₂	2210	^d —	61JOC2396
5-CO ₂ Et	2195	DCM	83DIS(B)(43)2557
5-COPh	2220	KBr	75LA2159
5-Ph	2150	DCM	83DIS(B)(43)2557
3-Diazo-1,2,4-triazole	2205	Acetone	74MI1
5-CO ₂ H	2240	Film	70KGS705
5-CO ₂ Me	2230	Film	70KGS705
5-Ph	2200	^d —	81DIS(B)(42)1892
5-(3-NO ₂ -Ph)	2200	Film	70KGS705
5-(4-NO ₂ -Ph)	2200	Film	70KGS705
5-Diazotetrazole	2275	NaCl	72JA1379

^a Other values have been reported for this compound (2040 cm⁻¹) and the diazonium chloride (2100 cm⁻¹) by Krautzberger and Kalter (61JPC624). However, the reviewers prepared both derivatives following carefully the same experimental conditions and found values, in CHBr₃, identical to those reported in this table.

^b Later, 2085 cm⁻¹ (KBr) and 2110 cm⁻¹ (DCM) were reported [75AG(E)103].

^c Later, 2110 cm⁻¹ (KBr and DCM) was reported [75AG(E)103].

^d Not reported.

observed in the 3-diazoisomers ($2065\text{--}2155\text{ cm}^{-1}$). In both series, electron-withdrawing substituents shift the bands to higher frequencies.

Benzocondensation of the pyrrole ring does not lead to any variation in diazo-group stretching and, in fact, in the 3-diazoindoles, IR bands are found at $2085\text{--}2123\text{ cm}^{-1}$.

Both 3- and 4-diazopyrazoles show strong bands between 2119 and 2222 cm^{-1} . In the 5-one series, additional conjugative effects substantially shift the stretching bands of the diazo group to lower frequencies [60CI(L)659; 62JA1399].

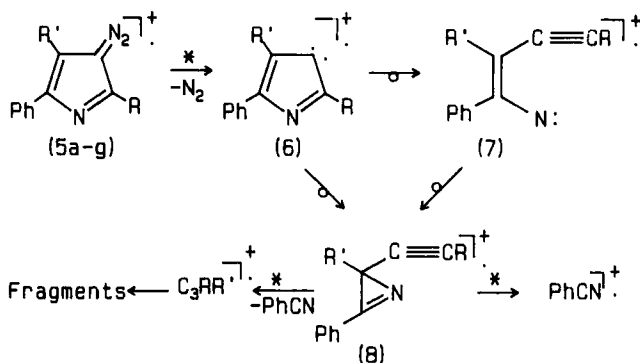
The diazo-stretching bands in 2-diazoimidazoles are found at lower wavenumbers ($2105\text{--}2247\text{ cm}^{-1}$) than those observed in 4-diazo-derivatives ($2140\text{--}2210\text{ cm}^{-1}$).

4-Diazo-1,2,3-triazoles absorb $2150\text{--}2220\text{ cm}^{-1}$, in a range that is close to that observed for the 4-diazoimidazoles, indicating that aza substitution in the 2-position of the ring does not lead to great variation in the relative contribution of the mesomeric forms. Instead, in the 3-diazo-1,2,4-triazoles, the absorption bands associated with the diazo group are found in the range of $2200\text{--}2240\text{ cm}^{-1}$, very close to that of aromatic diazonium salts (62JA1399). Moreover, the 5-diazotetrazole has a diazo band at 2275 cm^{-1} , indicating that the major contributions to the resonance hybrid are attributable to forms **3a** or **3b**.

Evaluation of the reported data shows an increasing diazo-stretching frequency with the introduction of aza substitution in the five-membered ring. At one extreme, there is diazocyclopentadiene, well represented by the mesomeric form **3c**, and at the other extreme, there is diazotetrazole, for which a diazonium type structure is more suitable. The conjugation between the diazo group and the heterocyclic ring decreases going from diazocyclopentadiene to diazotetrazole. This is due to the greater ability of the more electronegative heterocycles to accept the negative charge; the greater the delocalization of the negative charge in the ring, the higher the frequency of absorption, and the greater the contribution of triply bonded diazo forms. Although the vibrational relationship between diazoazoles and the corresponding diazonium salts has never been studied, a comparison of diazo triple bond structures (**3a** and **3b**) with a diazonium salt triple bonds reveals that a shift toward higher frequencies can be expected to proceed from the former to the latter (61JPC624). In fact, a shift of $\sim 60\text{--}100\text{ cm}^{-1}$ to higher frequencies is observed in the diazonium salts.

E. MASS SPECTRA

The behavior of diazoazoles on electron impact (EI) is little studied. However, the EI mass spectra (75 eV) of 2,4-substituted 3-diazo-5-phenyl-



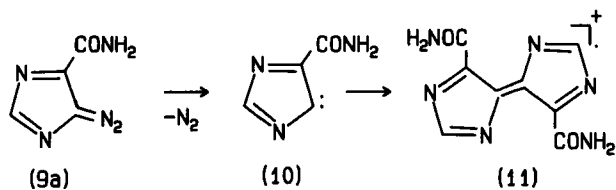
SCHEME 2. Structure 5: a, R = R' = Ph; b, R = 4-CH₃-Ph, R' = Ph; c, R = 4-OCH₃-Ph, R' = Ph; d, R = 3-OCH₃-Ph, R' = Ph; e, R = 2-OCH₃-Ph, R' = Ph; f, R = Ph, R' = H; g, R = 4-CH₃-Ph, R' = H. *, Metastable supported transition.

pyrroles (5) (Scheme 2) always show the molecular ions and undergo, as main fragmentation processes, the elimination of nitrogen followed by ring-opening reactions leading to benzonitrile, either as a neutral or charged species (87UP1). The proposed mechanism involves the isomerization of 6 to the 2*H*-azirine (8) by ring opening to nitrene (7) and subsequent heterocyclization, or by a concerted 6 → 8 rearrangement. The peaks, 26 daltons below the molecular ions, which are a general feature of these spectra, belong to the parent pyrroles as contaminants.

Although the mass spectrum of 4-diazoimidazole-5-carboxamide (9a) (Scheme 3) was not studied in detail, a radical ion corresponding to the imidazolylidene-imidazole (11) (a dimer of carbene 10 generated by nitrogen elimination from the diazoimidazole) was observed in the EI-promoted mass spectrum of this diazo compound as well as in those of 2-azahypoxanthine and of all imidazotetrazinones (84JMC196).

F. THERMODYNAMIC ASPECTS

A main feature about thermodynamic aspects in diazoazole chemistry regards the stability, or rather the lack of stability, of several diazoazoles



SCHEME 3

that make them difficult to handle. In fact, some could not be obtained analytically pure [60CI(L)659], or they were decomposed or were transformed during the recording of spectral data; determination of the structure was a main problem especially in early days.

2-Diazopyrroles are less stable and more sensitive to light than the 3-diazopyrroles (62JCS1638). In both series, electron-withdrawing substituents increase the stability of the diazo compounds so they can be stored for a longer period, even at room temperature, provided they are kept in the dark. All melt with decomposition. The 3-diazoindoles are very sensitive to light, which decomposes them with nitrogen evolution, producing a brown residue (06G56). The diazopyrazoles are light sensitive, and the 3-diazopyrazoles are also shock sensitive and piezersonic (87JOC5538). They can explosively decompose at their melting points (68JPS1044) or even several degrees above (66CB3350; 71JMC1245). Usually, the 4-diazopyrazoles are more stable than the corresponding 3-diazoisomers. In some cases, when bulky substituents are present, this can be attributed to steric inhibition of resonance that reduces the possibility of more extended conjugation (62JA1399).

The diazoimidazoles are light and shock sensitive and decompose or melt explosively over a wide temperature range (73JA2695; 73USP3770764; 87JOC5538). Generally, the 4-isomers are more stable than the corresponding 2-diazo derivatives; it is preferable not to dry them, but to use them in solution as soon as they are prepared (87JMC357). Nevertheless, 4-diazo derivatives, in which there is the possibility of intramolecular cyclization with the substituent in the 5-position even if stable under anhydrous conditions, easily cyclize in aqueous solution over a wide range of pH values [62JOC2150; 66CI(L)2197].

Both 3-diazo- and 4-diazo-triazoles are light and shock sensitive and explode when scratched [81DIS(B)(42)1892; 83DIS(B)(43)2557]. They can be stored in the dark at room temperature for several weeks without any apparent decomposition [81DIS(B)(42)1892; 87JOC5538]. However, whereas 4-diazo-1,2,3-triazoles are remarkably stable in solution [83DIS(B)(43)2557], 3-diazo-1,2,4-triazoles decomposed if kept in solution at room temperature for a few hours (87JOC5538), and in the case of 5-alkyl-3-diazo compounds, loss of nitrogen was observed even if their solutions were refrigerated [86DIS(B)(46)3052].

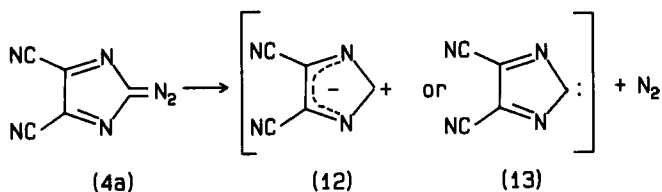
Diazotetrazole is extremely explosive (1892LA46). Aqueous solutions of diazotetrazole explode at 0°C, if more concentrated than ~2% (1892LA46). Ethereal solutions after standing at -70°C for 1 hr explode. The overcooling of the solution appears to be a critical factor because of the formation of crystals that separate as a suspension (72JA1379). The safest conditions were at 2-5°C using an excess of solvent. As long as the

diazo compound was kept in solution, no difficulties were encountered (75CRV242).

Studies leading to a less empirical evaluation of the stability of diazoazoles have been reported. Thus, labelled compounds were used to investigate the stability of diazoheterocycles with particular regard to the possibility of nitrogen interchange within the diazo group (76H1115). This process was observed in the case of aromatic diazonium compounds and could also be explained as proceeding via an intermediate diazirine derivative (78MI2). A diazirine, a valence isomer of the diazo compound, has been isolated in the indole series [75AG(E)103]. Therefore, it was supposed that an intermediate of this type could be involved in rearrangements of diazoazoles. However, in the only compound studied, 3-diazoindazole, it seems that rearrangement is not verified (76T725). Besides, for the only diazirine isolated, it was calculated that the activation energy for the dediazonium process is always lower than that of the process leading the valence isomer (75CB3326). Therefore, generally, the elimination reaction is favored.

Measurement of the half-life of diazoazoles in different media is reported with particular regard to 2-diazoimidazoles, for which evaluation of the stability is of primary importance in connection with biological screening tests. 2-Diazo-4,5-diphenylimidazole had a half-life of 4–12 min in organic solvents (65AAC469), whereas 2-diazo-4-R-imidazoles ($R = H, CH_2COOH$), with a half-life between 8 hr and 2.5 days, showed an increased stability in neutral aqueous media where they are present as neutral zwitterionic species of type **3**, according to pK_a values (87JMC2222).

Kinetic studies showed the rate of nitrogen elimination from compound **4a** (Scheme 4) is first order and correlates with the Y value of the solvent (79JOC1717). A slower rate of decomposition was observed in more polar media. This would seem to reflect a greater solvation of starting material, which retards the nitrogen-extrusion process in more polar media. If the intermediate is better represented by **12** rather than **13**, nitrogen elimina-



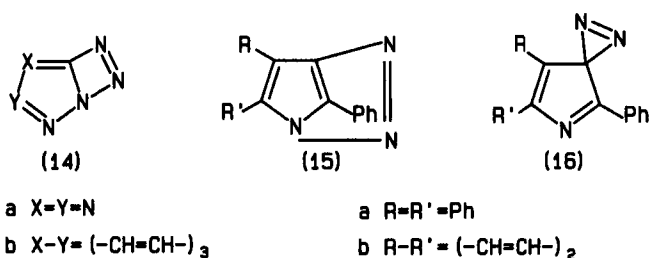
SCHEME 4

tion should be enhanced in polar solvents. However, the small entropy of activation, 1.4 entropy units (eu), suggests considerable solvation of the transition state as well as the ground state. Also, studies on the decomposition of the one-to-one complex between **4a** and 10-crown-6-ether, which is significantly more stable than **4a** alone, showed the rate of nitrogen elimination in benzonitrile, as expected, is slower than that of uncomplexed **4a**, whereas in acetic acid, it is slightly faster, suggesting that in the latter solvent, the complex is not tightly associated.

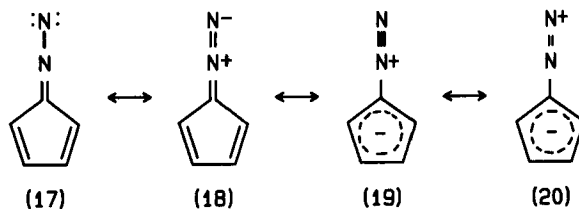
G. MESOIONIC AND OTHER STRUCTURES

At the end of the last century, those who synthesized the first diazoazoles had difficulties in assigning these compounds a structure that fully accounted for the observed physical and chemical properties. Thiele and Bamberger proposed the four-membered cyclic structure **14** (Scheme 5) for diazotetrazole and 3-diazoindazole, respectively (1892LA46; 1899CB1773), and the diazoazoles were regarded as anhydrides of the diazonium hydroxide since they were obtained from alkaline solution. Some years later, Italian chemists suggested cyclic structure **15** and a diazirine-type structure **16** for 3-diazoindoles and 3-diazopyrroles (04MI1; 05MI2). The true structure was not forthcoming until the synthesis of diazocyclopentadiene in 1953 (53JA5955). The diazocyclopentadiene was depicted as a resonance hybrid of the canonical structures **17–20** (Scheme 6). Of course, in forms **19** and **20**, the negative charge can be localized on each of the five carbon atoms.

In the same year, for the first time, a mesoionic structure of type **19** was proposed for a diazoazole (53AG442). Since then, several studies were carried out with the aim of proving the structure of the diazoazoles by



SCHEME 5



SCHEME 6

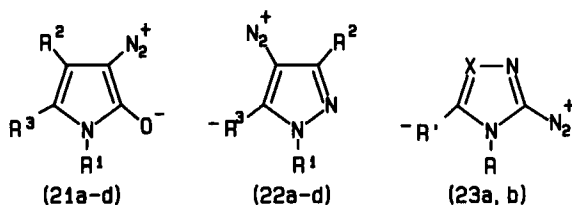
analogy with the carbocyclic diazo compounds. From all the experimental data reported in the previous sections of this chapter, the diazoazoles can be described as mesoionic compounds that are represented by a resonance hybrid of structures **3a–d**, heteroanalogues of **18–20**. In light of spectroscopic evidence, it can be seen that the diazirine-type cyclic structure **16**, proposed previously for the diazoazoles, actually represents a valence isomer of the diazo compound and, in fact, the diazirine isomer was isolated and characterized by photolysis of 3-diazoindoles [75AG(E)103] (see also Section III,A).

However, in the ground state, the main contributions to the resonance hybrid are due to forms **3a,b**. Their importance increases going from diazopyrroles to the diazotetrazole, so that the diazo structure with cumulated double bonds, which has been extensively employed as a shortened form for the diazoazoles, does not seem to depict them correctly any more. Therefore, in continuation of this review, the diazoazoles will be represented by structure **3a** unless other limiting forms better account for the observed reactivity. In fact, even the nitrene-like form, a heteroanalogue of **17**, which is the one with highest energy, has been invoked to explain the reactivity in some cycloaddition reactions (86CC1127).

A mesoionic diazo-type structure can be invoked also in the case of N-substituted azoles of type **21–23**, in which there is loss of proton from an enolizable group (such as OH or NHCOR) (Scheme 7). For these “unconventional” diazoazoles, the same considerations about the contributions of the different forms to the resonance hybrid are compatible.

H. DIAZO–DIAZONIUM EQUILIBRIUM

All azole diazonium salts and the corresponding diazocompounds can be converted into each other. Thus, neutralization or alkalinization of the



SCHEME 7. Structure 21: a, $R^1 = \text{CH}_2\text{-Ph}$, $R^2 = \text{CONH}_2$ [74LA1550], $R^3 = \text{H}$; b, $R^1 = \text{C}_4\text{H}_9$, $R^2 = \text{CONH}_2$, $R^3 = \text{H}$ [74LA1550]; c, $R^1 = \text{H}$, $R^2 = R^3 = (-\text{CH}=\text{CH}-)_2$; d, $R^1 = \text{CH}_3$, $R^2 = R^3 = -\text{CH}=\text{CH}-$ [75CB3326]. Structure 22: a, $R^1 = \text{Ph}$, $R^2 = \text{CO}_2\text{Et}$, $R^3 = \text{O}$ [78H(10)199]; b, $R^1 = \text{H}$, $R^2 = \text{Ph}$, $R^3 = \text{O}$ [62JA1399]; c, $R^1 = \text{Me}$, $R^2 = \text{Ph}$, $R^3 = \text{N}=\text{C}(\text{Ph})\text{O}$ [84JHC957]; d, $R^1 = R^2 = \text{Ph}$, $R^3 = \text{N}=\text{C}(\text{Ph})\text{O}$ [87MI1]. Structure 23: a, $X = \text{CH}$, $R = \text{H}$, $R' = \text{CH}_2\text{COO}$ [87JMC2222]; b, $X = R = \text{H}$, $R' = \text{COO}$ [70KGS705].

solutions of the salts with several inorganic bases, such as alkaline carbonates, bicarbonates, acetates, and hydroxides depending on the acidity of the heterocycle, allow isolation of the diazo compounds (see also Section IV,B). Recently, other organic bases, such as 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) or 1,5-diazabicyclo[4,3,0]non-5-ene (DBN), were employed to homogeneously release the free diazoazoles (87JMC357). These, in turn, can generate the diazonium salts by addition of acids. Only in the case of 4-diazo-3-phenylpyrazol-5-one (**22b**) was a different behavior observed: the diazo remained unchanged under acid conditions but dissolved in aqueous sodium hydroxide because of the presence in the nucleus of an acidic NH group [60CI(L)659].

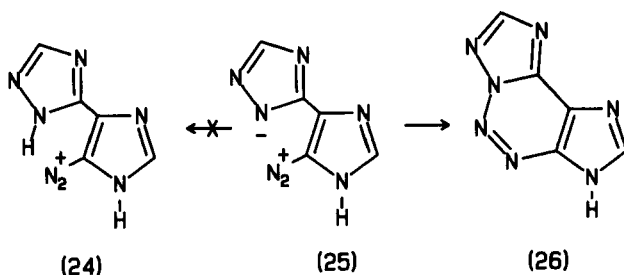
3-Diazopyrroles can be quantitatively converted into the corresponding diazonium chlorides if treated with anhydrous hydrochloric acid in dry solvents with strict control of the temperature, which must not rise higher than 5°C (05MI2; 61JOC3790). Other stable diazonium salts can also be isolated (10G411), but not with organic acids (23G795). Similar behavior was observed in the case of 3-diazoindoles (06G56).

3-Diazopyrazoles can be converted into very stable diazonium salts (chloride or bromide) upon treatment with the corresponding concentrated acid at room temperature (76JOC3781; 84JHC957). Stable diazonium tetrafluoroborate [87JOC5538], platinichloride, and aurichloride [14JCS(105)435] can be isolated. Only in the case of the unstable 3-diazopyrazole was it necessary to operate at low temperature and in non aqueous solvents (61CB1036).

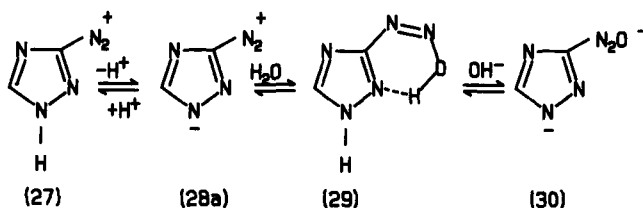
Imidazole-4-diazonium tetrafluoroborates can be prepared, and they show exceptional stability (73JA4619). In the imidazole series, however,

the diazo-diazonium equilibrium can be complicated by the possibility of intramolecular ring closure. Thus, in the case of 4-diazoimidazole-5-carboxamide (**9**), the diazonium salt is formed at pH = 1 [62JOC2150; 81JCS(P1)1433], whereas in the case of 4-diazoimidazole (**25**) the imidazo-triazolo-triazine (**26**), resulting from closure at the 1-position of the triazole ring, was formed in acid conditions instead of the expected diazonium salt (**24**) [66CI(L)2197] (Scheme 8).

The diazotriazoles can be isolated even under acid conditions because of the high mobility of the imino nitrogen; a consequence of the electron-poor heterocycle. In the 3-diazo-1,2,4-triazoles, the electronic effects of the substituents in the 5-position are important. In fact, when the electronegativity of this substituent is low (Me, Ph), it is possible to isolate the diazonium salts, and the diazo compounds are obtained only at higher pH values (70KGS705). These findings were also supported by studies on the coupling rates of the 1,2,4-triazole-3-diazonium cation and other heteroaromatic diazonium salts (86CJC1102). The logarithms of these rate constants were plotted against the chemical shift of that proton of the respective parent compound, which is replaced by the diazonium group in the diazonium ions. A good linear relationship was found in the pH range 4.01–5.97 for all the compounds with the exception of the triazole diazonium ion. The lower coupling rate was explained by the easy deprotonation of the iminic-ring nitrogen leading to the diazocompound, which is less electrophilic than the salt. However, the value of the chemical shift of the corresponding 1,2,4-triazole anion does not completely justify the initial discrepancy. Thus, adding water to **28a**, which lead to the diazo-hydroxide **29**, which is likely not electrophilic at all, was invoked. Moreover, when neutral solutions of **29** are treated with base, a red color appears because of the mono or disodium salts of the hydroxide [86DIS(B)(46)3052] (Scheme 9).



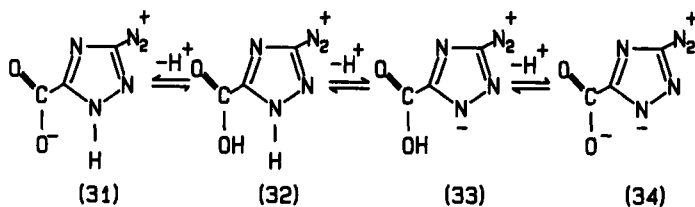
SCHEME 8



SCHEME 9

A particular case of diazo-diazonium equilibrium is that of 3-diazo-1,2,4-triazole-5-carboxylic acid (**33**), in which loss of the proton also can take place from the substituent (Scheme 10). This equilibrium was studied by UV and IR spectroscopy (70KGS705). In strongly aqueous acid media, the equilibrium shifted in the direction of **32**. As pH increased, the diazonium salt **32**, gives a diazotriazole that could be either **31** or **33**. The reduced intensities of the IR bands due to the heterocycle, which indicates an increased electron density in the ring due to loss of the imino proton, and the similarity with the UV and IR spectra of the corresponding diazo ester showed that loss of a proton happens from the ring nitrogen rather than from the carboxylic group. In weakly alkaline aqueous media, diazo **33** further loses a proton to give **34**. In fact, while the diazo-stretching band remains unchanged, bands of the un-ionized carboxyl disappear, and bands attributed to the carboxylate anion are found in the IR spectrum.

The diazo-diazonium equilibrium of the diazotetrazole represents a very special example. Although diazotetrazole has been known since the 19th century, it was not isolated until 1972 (72JA1379). However in that report, the structure of a diazonium salt was assigned to the explosive product isolated by ethereal extraction from the strongly acidic reaction solution. Actually, the isolated compound was the diazotetrazole, which is more likely to be extracted with ether. Moreover, upon thermolysis of the same compound in presence of gaseous reactants, neither hydrochloric acid nor chlorinated compounds were detected (72JA1379; 73JA4441; 77JA2627).



SCHEME 10

TABLE V
 pK_a VALUES OF DIAZOAZOLES

Compound	pK_a	Method*	Reference
3-Diazopyrazole 2,5-diMe	4.95 ± 0.05	S,P	74TL1609
2-Diazoimidazole	2.6 ± 0.1	P	74TL1609
3-Diazo-1,2,4-triazole	0.3 ± 0.1	S	74TL1609
4-Diazo-1,2,3-triazole	-0.4 ± 0.1	S	74TL1609
5-Diazo-tetrazole	-5.2 ± 0.1	S	74TL1609

* S, Spectrophotometric; P, potentiometric.

Some years later the same author arrived at the same conclusion by a mass spectrometric study of the same reaction, when, again, hydrochloric acid was not found as a product (79JA1303). Therefore, the tetrazole diazonium salt can exist only in extremely strong acid conditions as expected from the pK_a values.

The pK_a of some diazoazoles in aqueous solution at 0°C was experimentally determined by using either potentiometric or spectrophotometric methods (74TL1609). Data are shown in Table V.

The values were also calculated by using the Hammett equation $\Delta pK_a = \rho \sigma_m$, in which $\sigma_m = 1.76$ was used for the N_2^+ group. The experimental values are in good agreement with those calculated by using the Hammett equation, except in the case of 2-diazoimidazole for which a strong "ortho" effect should be considered. In fact, in the diazonium salts of all other azoles, it is always possible to suppose that the proton can be localized on a meta-ring nitrogen, whereas, this is impossible in the case of protonated 2-diazoimidazoles (74MI1). It was also observed that the diazonium group increased the acidity of the ring, in comparison with the unsubstituted azole, by about 10 on the pK_a scale (74TL1609).

III. Reactivity

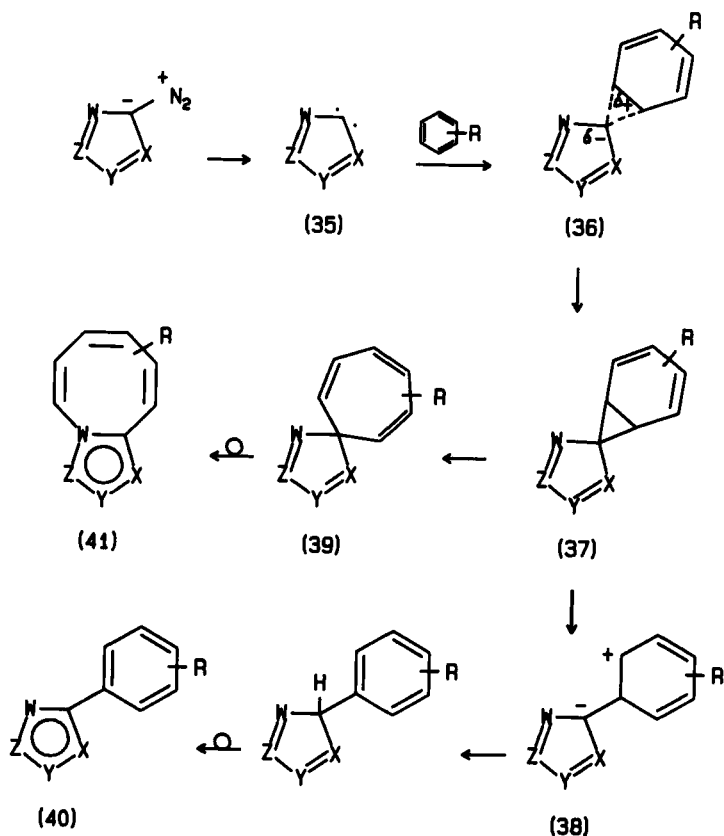
Because of the differences connected with the nature of the heterocyclic moiety, diazoazoles show quite a range of reactivities. To draw a synoptic picture of the reactivity of diazoazoles is not easy. In fact, the diazo-diazonium function can undergo very different types of reactions, and occasionally there is a lack of experimental data, either because the reaction was not studied or because the researcher could not isolate all the products. However, trends in the behavior reflect the electronic character of the different series.

A. THERMAL AND PHOTOCHEMICAL REACTIONS

The behavior of diazoazoles upon thermolysis and photolysis is very complex and widely varied, depending on the nature of the diazoheterocycle and on the medium. In this introduction, we will point out aspects common to all diazoazoles, whereas, the peculiar processes of each heterocycle will be discussed separately.

In all these types of reactions, the first step is always the formation of a carbenic species, either in singlet or triplet form; the first is more prevailing. Hückel molecular orbital (HMO) calculations showed that the spin states of azolyldenes depend mainly on the interaction of an empty σ orbital at the carbenic center with a filled sp^2 -orbital of an adjacent nitrogen atom, whenever possible [83DIS(B)(44)1113]. Carbenes not having a heteroatom adjacent to the carbenic center (3*H*-pyrrolylidene, 3*H*-indolylidene and 4*H*-pyrazolylidene) are predicted to be ground-state triplets, whereas all other azolyldenes are ground-state singlets. The carbene can then either react with other species present in the reaction medium or decompose, by ring opening and/or loss of nitrogen. The latter behavior is a general feature for the diazotetrazole and is also observed in all diazoazoles in which cleavage of the nuclear N—N bond adjacent to the carbenic center is possible.

In thermolysis and photolysis in cyclohexane, all diazoazoles, except diazoindazole (see Section III,A,4), gave the corresponding cyclohexyl derivative resulting from insertion by the singlet carbene into the C—H bonds and/or from abstraction–recombination by the triplet carbene into cyclohexane. Thermolysis and photolysis of diazoazoles in benzene derivatives showed different patterns that are related to the electronic character of the azoles and of the substituents in the benzene, and are essentially independent of the method used to generate the carbene **35** (Scheme 11). A simple mechanism leading to the reaction products involves selective electrophilic attack of the singlet carbene **35** on the π system of the substituted benzene to give the spironorcaradiene **37**. Studies on the competitive reactivity of benzene derivatives and electron spin resonance (ESR) measurements in the imidazole and triazole series, indicating the ground state singlet of the intermediate carbene, were reported [81DIS(B)(42)1892; 86TL901]. These data supported the spironorcaradiene. The rate-determining step is the exothermic addition of singlet **35** in its p^2 state to benzene through a transition state of type **36**, which has limited dipolar character. The key intermediates of these reactions, the spironorcaradienes **37**, can collapse either to the dipolar σ complex **38**, by heterolytic cleavage of the cyclopropane moiety, or to the spirocycloheptatriene **39**, by electrocyclic isomerization. [1,5]-Sigmatropic rearrange-



SCHEME 11

ments of intermediates **38** and **39** lead to the ring substitution products **40** and ring expansion compounds **41**, respectively.

The formation of the ring substitution products **40** was observed in all the series. Fast conversion of spironorcaradiene **37** to dipolar intermediate **38** is driven by the electronic effects of the substituents rather than steric effects, since the spiro structures **37** are not highly hindered by R. Thus, electron-releasing groups give rise to ortho and para substitution and electron-attracting groups originate meta substitution products. This regioselectivity does not parallel high substrate selectivity, as in aromatic substitutions by electron-deficient reagents. In fact, azolylium **35** showed small differences in overall reactivity, behaving as an unusually unselective electrophile. However, anomalous behavior was observed in substituents having lone pairs on atoms bound to the benzene, in that a

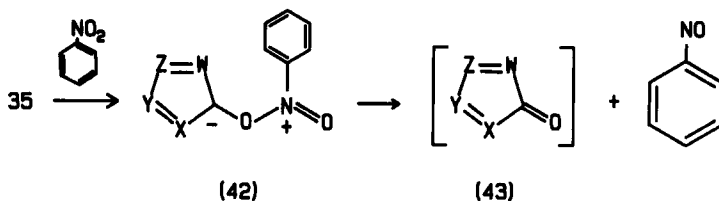
high ortho-para directing power was found. Such a high ortho substitution process becomes understandable if additional processes involving ylidic coordination of the carbene **35** with the aromatic substituent are considered. These ylide intermediates can be isolated in some cases and can also evolve through different pathways.

The occurrence of ring expansion processes, leading to **41**, was observed only in the pyrrole and pyrazole series in reactions with deactivated benzenes. A major mechanistic point is that groups, both highly conjugating and electron withdrawing, retard the dipolar ring-opening of **37** to the σ complex **38** and, at the same time, accelerate the electrocyclic isomerization accentuating the formation of ring-expansion products. Diazopyrazoles were less selective than diazopyrroles; in fact, the latter exclusively gave ring substitution with electron-donor substituents and ring expansion with benzene and electron-attracting substituents. Diazopyrazoles, instead, always gave a mixture of the two products, and the main one always originated by the ring substitution pathway except in the case of nitrobenzene, in which the products were obtained in comparable yields. The reason is found in the heterocyclic moiety of the spironorcaradiene structure **37**. In fact, the allowance of the negative charge in the σ complexes is easier in the pyrazole ring, and the pyrazole nucleus is less available to act as an electron donor system in the rearrangement of **39** to **41**.

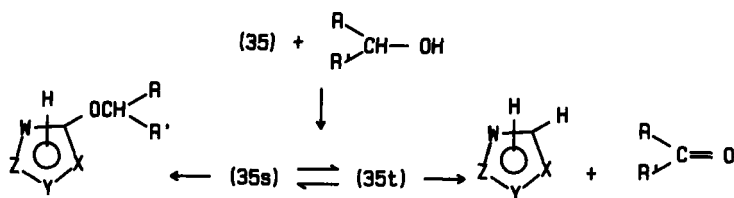
Most electrophilic carbenes, such as 2*H*-imidazolyliidenes and 3*H*- and 4*H*-triazolyliidenes, in nitrobenzene gave rise to deoxygenation processes involving the intermediacy of the ylide **42**, which decomposed to nitrosobenzene and **43** (Scheme 12). However, the azolones **43** are too unstable to be detected or trapped in the reaction conditions.

As predicted, in reactions of 3-diazopyrroles, 3-diazoindoles, and 4-diazopyrazoles with benzene derivatives, azolylidene **35** also reacted in its triplet state to give the parent heterocycle by abstraction-recombination processes.

In the thermolysis and photolysis in alkenes, the diazoazoles gave allylic insertion as a general reaction, although vinylic insertion and addition to give spirocyclopropane adducts were also observed. Thermolysis and



SCHEME 12



SCHEME 13

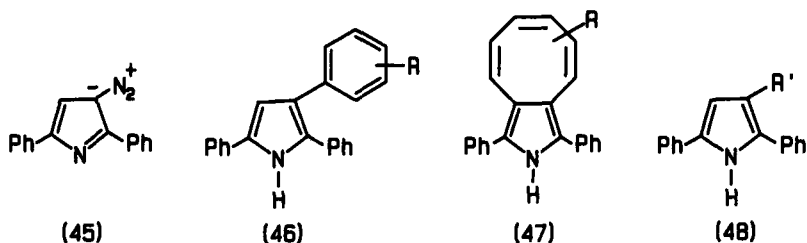
photolysis of diazoazoles in alcohols led to two competitive processes: The oxidation–reduction reaction, leading to the corresponding carbonyl compound and to the parent heterocycle, and the nucleophilic substitution process. These reactions were interpreted in terms of an equilibrium between the singlet and triplet states of the carbene in which **35t** leads to a hydrogen abstraction process, and **35s** reacts with the oxygen of the alcohols to give the alkoxy derivatives (Scheme 13). At the same time, the electrophilic character of the azolyldiene plays an important role in these competitive processes. In fact, in the pyrrole series, the carbene is not electrophilic enough to attack the oxygen of the alcohol, so the main process is the redox reaction. As the electrophilicity of the carbene increases with increasing azasubstitution, the extent of the oxidation–reduction process lowers, and the nucleophilic reaction becomes the main pathway.

Photolysis of azolediazonium tetrafluoroborates, by the method of Kirk and Cohen (73JA4619), is a general reaction in the pyrazole, imidazole, benzimidazole and triazole series and is of synthetic interest to obtain fluoroazoles.

1. Diazopyrroles

Thermolysis and photolysis in pyrrole series concerns only reactions of 3-diazo-2,4,5-triphenylpyrrole (**44**) and of 3-diazo-2,5-diphenylpyrrole (**45**) (Scheme 14). Exposure of **44** to sunlight resulted in loss of nitrogen [23G795]; photolysis in benzene gave 2,3,4,5-tetraphenylpyrrole, whereas irradiation in dry methanol led to 2,3,5-triphenylpyrrole [68JCS(C)1601].

The thermolysis or photolysis of **45** in benzene, substituted by electron releasing groups, resulted in selective ortho and/or para substitution, which lead to compounds **46** (79JA2198; 84JOC62). In these reactions, hydrogen abstraction, leading to 2,5-diphenylpyrrole (**48**) ($R' = H$), was also observed, and in the case of toluene and cumene, reaction with the substituent also took place, leading to the corresponding 3-substituted-2,5-



SCHEME 14

diphenylpyrrole **48**. The mechanism leading to **48** is not clear. These reactions were interpreted in terms of an equilibrium between the singlet and triplet states of the carbene in which the singlet form could insert into C—H bonds, and the triplet form could effect hydrogen abstraction with subsequent recombination and/or reduction (Table VI).

Reactions of **45** with benzene, and benzene substituted by electron-withdrawing groups gave the ring-expanded cycloocta[*c*]pyrrole derivatives (**47**) as the major products. The ring-expanded products were not formed either in the photolysis and thermolysis of **45** in benzene derivatives and acids, or upon photosensitization. Thus, irradiation of **45** in benzene–trifluoroacetic acid led to **48** ($R' = \text{Ph}$) in high yield (79JA2198; 84JOC62). Similarly, in anisole and in benzonitrile, the ortho and para isomers **46** were formed in a 1 : 1 ratio. The photolysis or thermolysis of the

TABLE VI
PRODUCTS (YIELD %) OF 3-DIAZO-2,5-DIPHENYLPYRROLE WITH
MONOSUBSTITUTED BENZENES^a

R	Reaction condition ^b	46			47	48 ($R' = \text{H}$)	Reaction with R
		<i>o</i>	<i>m</i>	<i>p</i>			
OMe	T/P	—	—	50/43	—	16/9	—
CH(Me) ₂	T/P	—	—	—	—	48/46	42/43 ^c
Me	T/P	14/11	—	14/11	—	14/6	14/11 ^d
H	T/P	—	—	—	73/31	—	—
CN	T/P	—	—	—	47/36 ^e	—	—
NO ₂	T	—	10	—	32 ^f	—	—

^a References, 79JA2198; 84JOC62.

^b T, Thermolysis; P, photolysis.

^c 3-(1-Methyl-1-phenylethyl)-2,5-diphenylpyrrole.

^d 3-Benzyl-2,5-diphenylpyrrole.

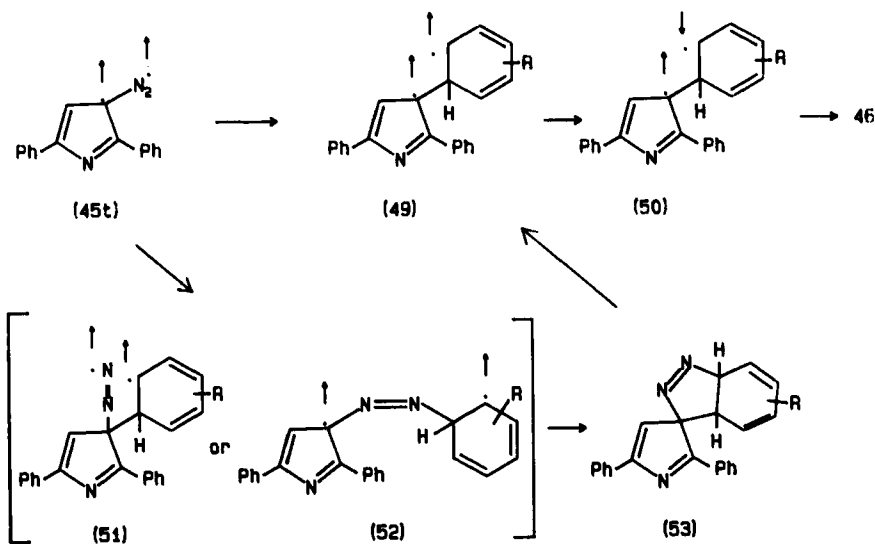
^e Mixture of 4-, 5-, and 6-cyano isomers.

^f Mixture of 4- and 6-nitro isomers (14%) and 5-nitro isomer (18%).

diazonium salt seems to be a reliable method for pyrrylation of aromatic rings and appears to be of the free-radical type.

The behavior of **45** upon photosensitization in benzene and benzonitrile is different from that previously mentioned. In fact, the photosensitization of **45** with thioxanthen-9-one gave the ortho-substituted products **46**, while the ring-expansion process was not observed (79JA2198; 84JOC62). For the photosensitized substitution, two possible mechanisms were suggested. The first involves the generation of triplet 3-diazo-2,5-diphenylpyrrole (**45t**), its decomposition to the triplet carbene, and its addition to the aromatic substrate to form the triplet diradical **49** (Scheme 15). Inter-system crossing to the singlet diradical **50**, hydrogen migration, and further [1,5] sigmatropic rearrangement give the substitution products **46**. The second mechanism involves the attack of **45t** on the aromatic ring, with spin inversion leading to intermediate **51** or **52**, and ring closure giving pyrazoline **53**. Loss of nitrogen gives the diradical species **49**, which rearranges to the product as in the preceding mechanism. The focal point of the proposed sequences is the conversion of **49** to **50** and rearrangement, rather than the ring closure to spironorcaradiene of type **37**. Nevertheless, the second mechanism seems to be the most probable, since the formation of triplet carbene from **45t** by loss of nitrogen is quite unusual (71MI1).

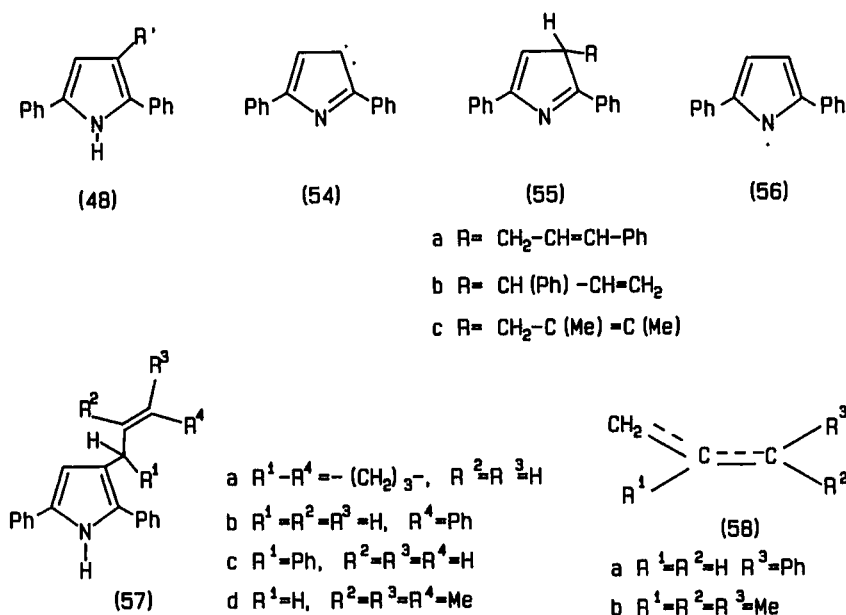
Unlike many carbenes, pyrrolylidene **54** does not add to olefins to give cyclopropanes. Thus, thermolysis or photolysis of **45** in cyclohexene,



SCHEME 15

allylbenzene, and 2,3-dimethyl-2-butene gave the 3-allylallyllyllyl-substituted pyrroles **57a-d** together with comparable amounts of **48** ($R' = H$) in the first two reactions (84JOC62) (Scheme 16). Although it is not possible to conclude whether **57a**, obtained upon reaction of **45** with cyclohexene, is formed by allylic insertion on cyclohexene by **54s**, the formation of **57b,c** is indicative of (i) abstraction of the methylene hydrogen from allylbenzene by **54t**, (ii) recombination of **56** and radical **58a** at C-1 or C-3, to give **55a** and **55b** respectively, and (iii) isomerization of the latter structures. The absence of **48** ($R' = H$) as product in the reaction between **45** and 2,3-dimethylbutene suggests that the formation of **57d** occurs by direct insertion of **54s** into C—H of 2,3-dimethylbutene, rather than by selective recombination of **56** with **58b** at C-1, leading to **55c** and subsequent rearrangement.

In the thermal decomposition of **45** in aniline and *N*-methylaniline, the carbene **54** showed electrophilic reactivity together with hydrogen abstraction ability (84JOC62). In fact, **48** [$R' = NPh, N(Me)Ph$], products of *N*-pyrrylation of anilines, together with **48** ($R' = H$), a product of hydrogen transfer to **54**, were obtained. In this case, aromatic substitution, typical of electron-rich benzene derivatives, was not observed. The formation of both *N*-pyrrylated anilines, evidence of involvement of **54s**, and the



SCHEME 16

hydrogen abstraction product suggests that the spin inversion of singlet to triplet takes place, to a large extent, even in the nucleophilic environment.

Although **45** in primary and secondary alcohols is stable at room temperature for several days, at higher temperatures or upon irradiation, it gives the reduction product and the corresponding aldehydes or ketones (84JOC62). Thus, **45** in benzyl alcohol and in 2-propanol gave benzaldehyde and acetone, respectively, together with a comparable amount of **48** ($R' = H$). The electrophilic reactivity of **54s** against the alcohols was only observed with methanol to give **48** ($R' = OMe$), but was observed, to a smaller extent, than for the oxidation–reduction of **54t** to formaldehyde and **48** ($R' = H$) (1 : 2.25). Probably alcohols are not sufficiently nucleophilic to react readily with **54s** to give 3-alkoxy derivatives, and the spin inversion to **54t** takes place to give the abstraction product. The possibility that the methoxy ether **48** was formed through the diazonium salt was demonstrated by irradiation of diazo compound **45** in methanol and trifluoroacetic acid, which gave the same products but in a ratio of 4 : 1. Moreover, photolysis in 2-propanol/trifluoroacetic and in acetic acid gave the two compounds **48** [$R' = OCH(Me)_2$ and $R' = H$ in a ratio of 1 : 1.3] and **48** ($R' = OAc$ and $R' = H$ in a ratio of 3 : 1) respectively.

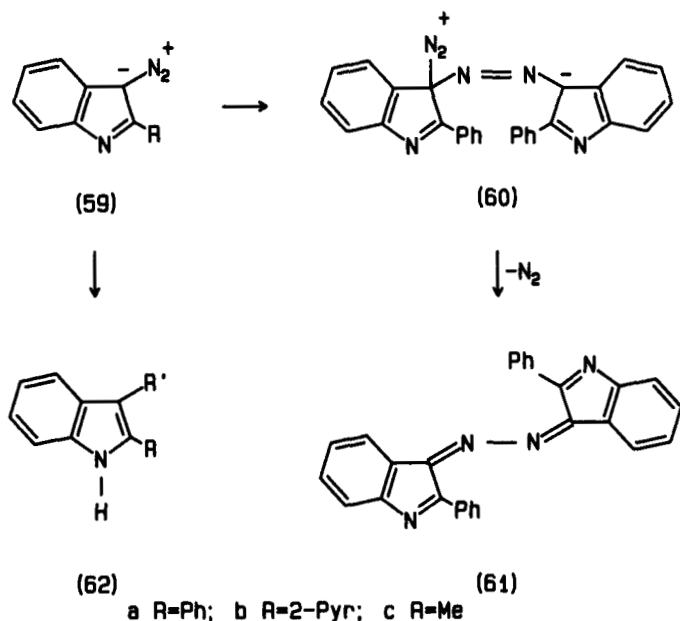
2. Diazoindoles

3-Diazo-2-R-indoles (**59**) are remarkably stable to thermolysis and are recovered unchanged after refluxing in benzene [74YZ23; 85JCR(S)402] (Scheme 17). However, prolonged thermolysis (48 hr) of **59a** in benzene gave 3,3'-diazinindole (**61**) [85JCR(S)402], probably by a self-coupling reaction of the diazo compound that included the formation of **60** and subsequent evolution of nitrogen. The reaction time was reduced upon addition of catalytic quantities of hydroquinone (74YZ36), but in this case, derivatives **62** ($R' = H$ and $R' = Ph$) were obtained either by hydrogen abstraction or C—H bond insertion.

Irradiation of **59a,c** in benzene gave the corresponding 3-phenylindoles **62** ($R' = Ph$) (66LA17). In the case of the 3-diazo-derivative **59a**, a dark red dye having structure **61** was also isolated. Photolysis of **59a** in anisole gave the para substitution products **62** ($R' = 4-OMe-Ph$) whereas in benzonitrile or methyl benzoate, only dark red oily mixtures were obtained.

Thermolysis of **59a,b** with electron-poor alkenes **63** gave the 1 : 1 syn and anti mixture of the spirocyclopropane adducts **64** [85JCR(S)402] (Scheme 18).

Photolysis of 3-diazoindole **59a** in cycloalkenes, via the addition of carbene **65** to the cycloolefine, gave rise to cyclopropane adduct **66**, which can rearrange to indolenines **68** or **69** and then to indoles **70** (66LA17).

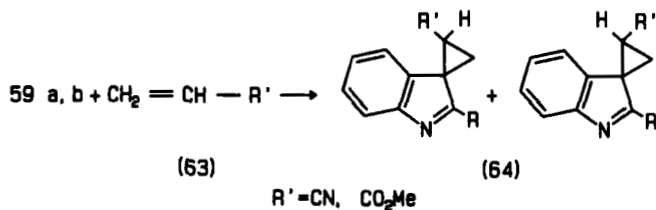


SCHEME 17

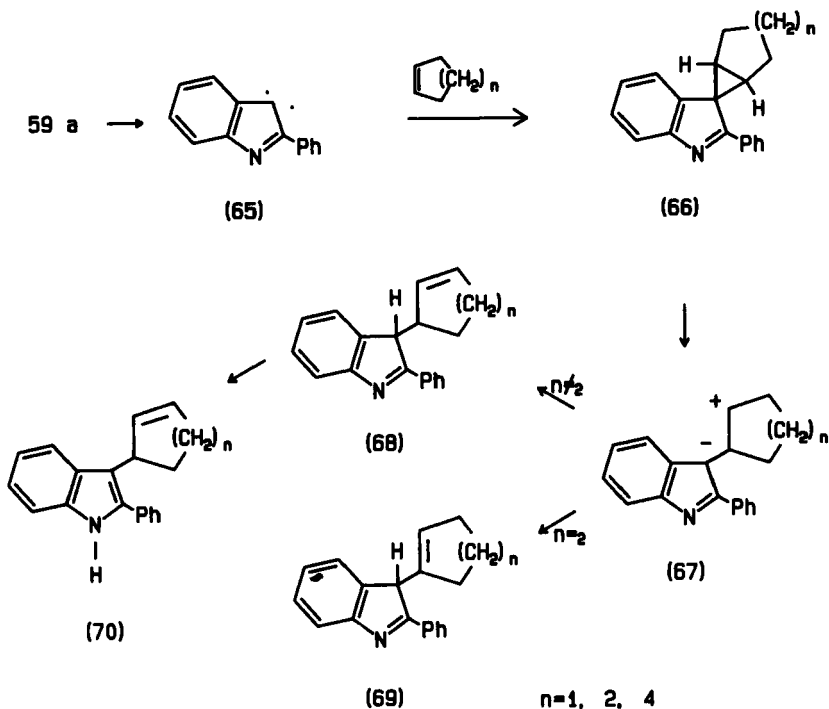
Aside from compounds **70**, depending on the ring size, derivatives **66** (when $n = 4$) and **69** (when $n = 2$) were also isolated (Scheme 19).

Photolysis of **59a** in alcohols (ethanol or isopropanol) gave the corresponding indole **62** ($R' = H$), by reductive diazo cleavage, together with acetaldehyde or acetone (66LA17).

The behavior of the "unconventional" 3-diazo-2-oxoindoles **21c,d** on photolysis and thermolysis needs to be mentioned separately because **21c,d** show a reactivity that is somehow different from that observed in indole series.



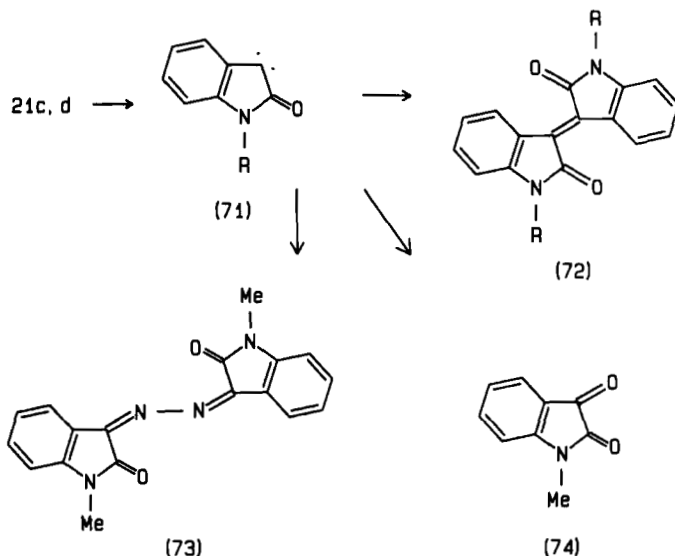
SCHEME 18



SCHEME 19

Thermolysis of **21c** in a sealed tube in benzene gave **72** ($R = H$) (16CB1923), while, by refluxing in absolute ethanol, **21d** was mainly recovered unchanged, and only traces of **72** ($R = Me$) and **73** were detected (64JOC3577) (Scheme 20).

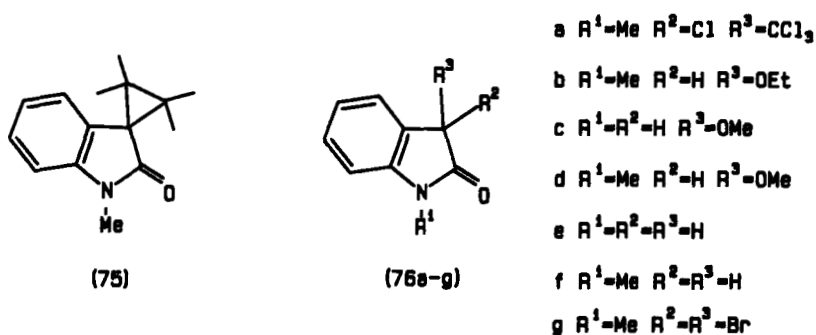
Thermolysis of **21d** in the presence of oxidizing agents gave 1-methylisatine (**74**) in addition to **72** ($R = Me$) and **73**. The same products were obtained upon photolysis in hexane at room temperature in the presence of air. These reactions demonstrated the electrophilic nature of the intermediate singlet carbene **71** by analogy with the behavior, in the same reaction, of dichlorocarbene and 9-diazafluorene (63JOC2460). It is likely that **72** could be formed either from the direct dimerization of two singlet oxindolylidenes **71** or from the reaction of the negative ipso carbon of the diazoindole with the carbene, followed by expulsion of nitrogen. Compound **73** could be obtained by electrophilic attack of the singlet carbene on the terminal nucleophilic nitrogen of another molecule of the diazo, but we think that a mechanism similar to that already shown in Scheme 17 is more likely.



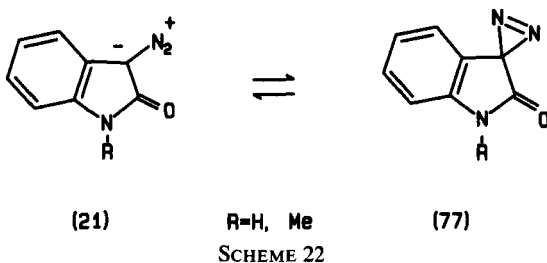
SCHEME 20

Photolysis of **21d** (see earlier **21**) in alkenes (cyclohexene, 1,1-diphenylethylene) always gave the cyclopropane derivatives **75** by a cis addition of the singlet carbene (64JOC3577) (Scheme 21).

Irradiation of diazo **21d** in carbon tetrachloride gave, in addition to **72** ($R = \text{Me}$) and **73**, the 3-chloro-3-trichloromethyl-1-methyloxindole (**76a**) (64JOC3577). Since the photolysis in carbon tetrachloride under comparable conditions produces, in the primary step, CCl_3 radicals and chlorine atoms (63JOC3442), in the formation of **76a** and probably in the reaction with oxygen to give **74**, the carbene **71** shows biradical properties in the



SCHEME 21

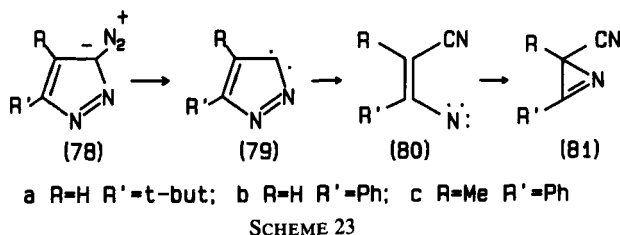


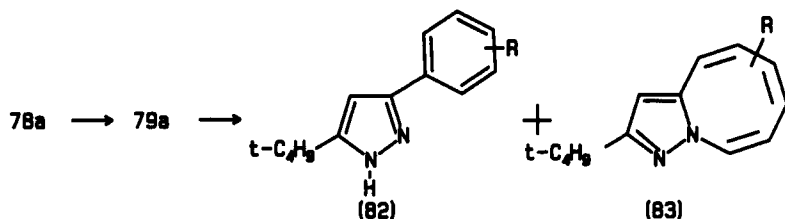
ground state. This suggests that the singlet and the triplet forms have very close energies and may be readily interconvertible.

Photolysis of **21d** under nitrogen in absolute ethanol gave 3-ethoxy-1-methoxyindole (**76b**) (64JOC3577). Irradiation of **21c,d** in methanol led to 3-methoxyindoles **76c,d** and oxindoles **76e,f** as main products [75AG(E)103; 75CB3326]. If the reaction was prematurely interrupted, it was possible to isolate, by chromatography, the diazirine **77** (Scheme 22) as a yellow photolabile product, which upon standing as a solid or in solution gives the red starting compound. This represents the sole photochromic-thermochromic equilibrium involving a diazoheterocycle and its valence isomer diazirine. Theoretical routes for this process were discussed, and it was found that the isomerization could involve mechanisms of ring closure and ring opening or elimination and readdition of nitrogen. A consideration of the energy and symmetry of the orbitals led to the conclusion that the latter mechanism seems more likely (75CB3326).

3. Diazopyrazoles

a. *3-Diazopyrazoles*. Vacuum pyrolysis of 3-diazopyrazoles **78** led to 2*H*-azirines **81** (77JA633) (Scheme 23). Such a decomposition seems of general and synthetic interest. The proposed mechanism involves the formation of 3*H*-pyrazolyldienes **79**, ring opening to the nitrenes **80**, and





SCHEME 24

subsequent heterocyclization and/or concerted rearrangement of **79**. Formation of **81** was also observed in the photolysis of **79c** in cyclohexane that, however, mainly led to the corresponding cyclohexylpyrazole. This occurred prior to the carbenic rearrangement (77JA633).

Thermolysis and photolysis of 5-benzoyl-3-diazo-4-phenylpyrazole in benzene afforded the corresponding ring substitution-compound [60CI(L)659]. Thermolysis and photolysis of **78a** in benzene derivatives always gave the ring substitution-products **82** and the ring expanded-product **83** (79TL4697) (Scheme 24). The large extent of the ortho substitution processes observed in these reactions become understandable if additional processes involving ylidic coordination of the carbene **79** with the substituent ($R = \text{OMe}, \text{Cl}, \text{CN}$) are considered (Table VII).

Photolysis or thermolysis of 3-diazopyrazoles with nucleophiles generally led to addition to the carbene species. Thus, in diethyl ether, compounds **84** and **85** (Scheme 25) were obtained in ratio 3 : 2 (77JA633). This reaction, leading to 1,2- and 1,3- adducts, is quite unusual since carbenes

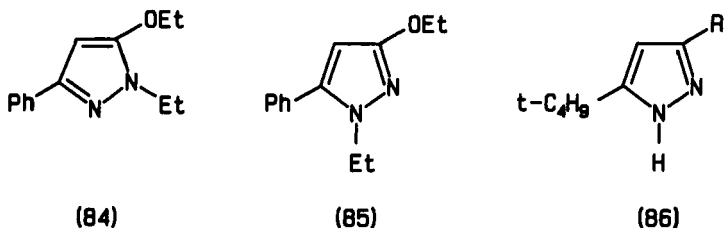
TABLE VII
PRODUCTS (YIELD %) OF 5-*t*-Butyl-3-DIAZO-PYRAZOLE WITH
MONOSUBSTITUTED BENZENES^a

R	Reaction condition ^b	<i>o</i>	82 <i>m</i>	<i>p</i>	83	Reaction with R
OMe	T	51	—	39	trace	^c
Me	T	64	—	29	trace	—
H	T/P	85/90	85/90	85/90	5/10	—
Cl	T	56	—	29	9	—
CN	T	51	20	13	16	—
NO ₂	T	trace	30	12	40	—

^a References, 77JA633; 79TL4697.

^b T, Thermolysis; P, photolysis.

^c 3-*t*-butyl-1-methyl-5-phenoxy-pyrazole, yield not reported.



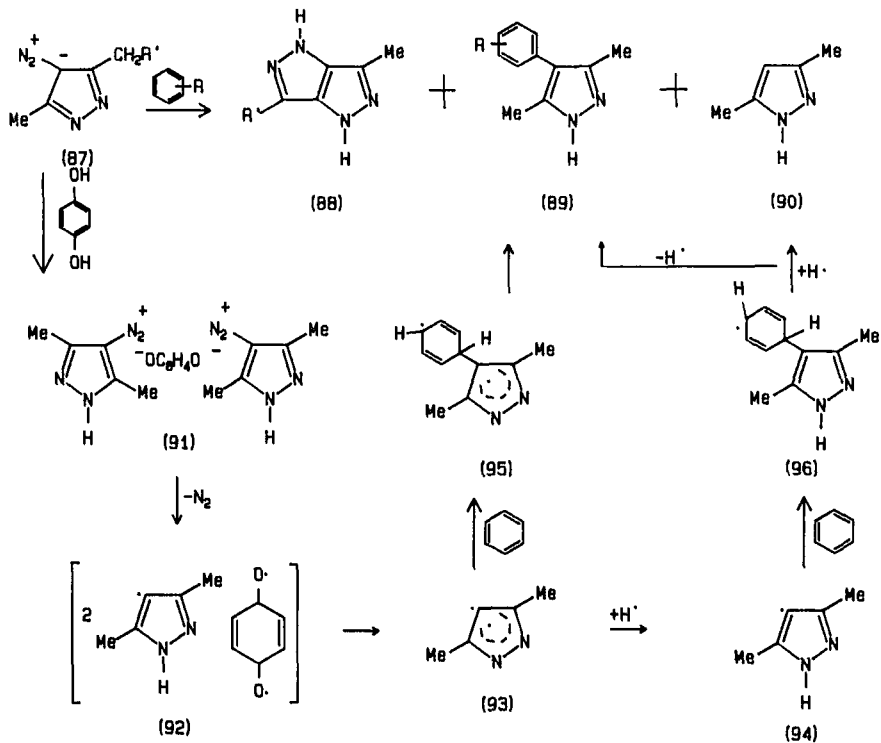
SCHEME 25

cleave ethers at oxygen to give 1,1 derivatives (71MI2). Attack of the electrophilic singlet carbene on the ether oxygen leads to an oxonium ylide that isomerizes to **84** and **85**. This transformation does not occur by successive [1,5] sigmatropic shifts since **84** is stable under the reaction conditions. Conversion to **84** and **85** can then be envisaged as ionization-recombination or bimolecular processes.

Thermolysis of **78a** in methanol yielded compounds **86** ($R = \text{OMe}$ and $R = \text{H}$) in a 1 : 1 ratio (77JA633). In this case, the nucleophilic substitution process becomes more important because of the increased electrophilicity of the carbene.

Photolysis of 5-benzoyl-3-diazo-4-phenylpyrazole in aqueous acetone only afforded the corresponding dediazoniated product (62JA1399).

b. 4-Diazopyrazoles. The behavior of 4-diazopyrazoles on thermolysis and photolysis is slightly different from that of the 3-isomers. In fact, thermolysis of **87** ($R' = \text{H}$) in benzene derivatives afforded the 4-arylpyrazoles **89** as the main products, as already observed for the 3-diazo series (73TL1199; 74YZ36) (Scheme 26). However, instead of the ring-expanded derivatives, compound **88** ($R' = \text{H}$) (in benzene) and the reduction products **90**, especially when $R = \text{Me}$, OMe , and Ac , were obtained. The observation that catalytic amounts of hydroquinone accelerated the reaction and increased the yields of **89** led to a postulated radical mechanism which involves the preliminary formation of the salt **91**, isolated from a chilled acetone solution of the diazopyrazole and hydroquinone. Compound **91**, following loss of nitrogen, gives rise to the radical-pair intermediate **92**, disproportionating to hydroquinone and **93**. The latter either adds to benzene to give the diradical species **95**, which, by hydrogen migration yields **89** or by hydrogen abstraction is converted into **94**. This intermediate in turn adds to benzene with formation of **96**, which transfers a hydrogen to **94**, giving **89** and **90**. That the intermediate of type **95** plays an important role to originate the products **89**, was actually also proposed for the photosensitized reaction mechanism in the pyrrole series (see scheme



SCHEME 26

TABLE VIII
PRODUCTS (YIELD %) FROM THERMOLYSIS (T) OF 4-DIAZO-2,5-DIMETHYLPYRAZOLE IN AROMATIC SOLVENTS WITHOUT (T) AND WITH HYDROQUINONE^a (H) (74YZ36)

Solvent	Reaction condition	<i>o</i>	89 <i>m</i>	<i>p</i>	90	88
PhOMe	T/H	6/12	—	4/7	28/42	—
PhMe	T/H	5/10	—	2/4	16/28	—
Benzene	T/H	36/70	36/70	36/70	12/10	25/—
PhCl	T/H	43/48	—	24/29	tr/tr	—
PhCOMe	T/H	13/15	3/4	3/4	21/28	—
PhCN	T/H	53/57	10/11	11/11	tr/tr	—
PhNO ₂	T/H	36/39	10/11	11/12	tr/tr	—
Thiophene	T/H	47/67 ^b	47/67 ^b	47/67 ^b	tr/tr	—

^a Addition of hydroquinone decreased by 2–15 times the reaction time.

^b α -Substitution.

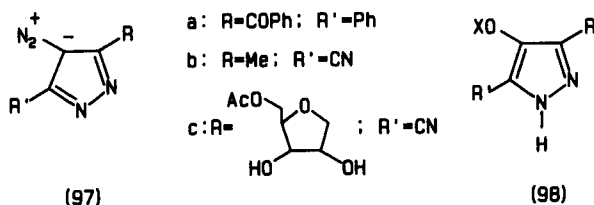
15) and for the homolytic ring opening of the intermediate pyrazole spironocaradiene of type **37**, although in those reactions its intermediacy seemed less probable [79TL4697; 84JOC62]. Also, photolysis of **97a** in benzene gave quantitative yields of the corresponding 4-phenyl derivative [60CI(L)659] (Table VIII).

Photolysis of 4-diazopyrazoles with nucleophiles led to the corresponding 4-alkoxy derivatives of type **98**. Thus, 4-diazopyrazoles **97a–c** irradiated in aqueous acetone gave good yields of the corresponding 4-hydroxy derivatives **98** ($X = H$) [60CI(L)659; 81JCS(P1)2374] (Scheme 27). Compound **97a**, irradiated in acetic acid/acetic anhydride, led to the 4-acetoxy derivative **98** ($X = Ac$) [60CI(L)659]. Photolysis of **97c** in water/dioxane and traces of acids, instead, gave the corresponding dediazoniated product [84JCS(P1)2367].

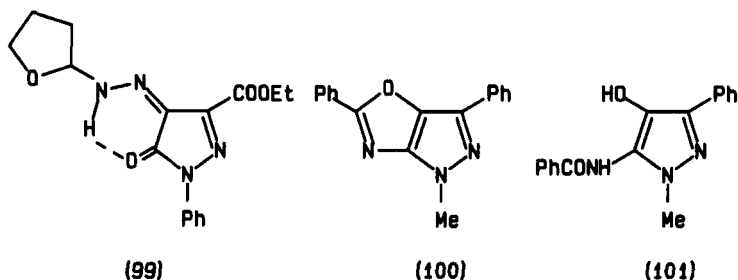
Thermolysis of **87** ($R' = H$) in alcohols (EtOH, PhCH₂OH, iso-C₃H₇OH, PhCHOHPh, PhCH=CHCH₂OH) led to the corresponding aldehydes or ketones and a comparable amount of pyrazole **90** (74YZ31). The yields are generally good if no other solvent is used, but in the presence of water or organic solvents, the yields are lower. The addition of a catalytic amount of hydroquinone was effective in increasing the yields and reducing the reaction time.

The unconventional 4-diazopyrazoles of types **22** are generally very resistant to thermolysis [60CI(L)659; 74YZ36; 78H(10)199] and brief photolysis [78H(10)199; 84H(22)2309]. On prolonged exposure to UV light, diazopyrazole **22a** decomposed in tetrahydrofuran (THF) giving, as the only isolable product, the addition compound **99** (Scheme 28) with retention of nitrogen [78H(10)199]. On the other hand, 4-diazopyrazole **22c**, irradiated under a variety of conditions (solid state, and neutral or basic solutions), gave, together with traces of the hydroxy compound **101**, the derivative **100** which was obtained by intramolecular nucleophilic ring-closure [84H(22)2309].

Thermolysis in benzyl alcohol of 4-diazopyrazole **22b** gave the corresponding 4-benzyl derivative [60CI(L)659]. The reaction goes through the



SCHEME 27



SCHEME 28

preliminary redox process leading to benzaldehyde and the dediazoniated pyrazole, which then undergoes reductive benzylation.

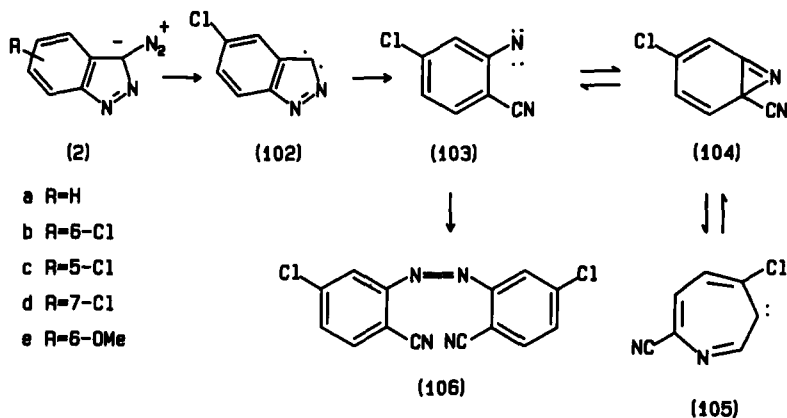
c. *Pyrazole Diazonium Salts.* Photolysis of pyrazole-3-diazonium and 3,5-dimethylpyrazole-4-diazonium tetrafluoroborates, by the method of Kirk and Cohen, gave the corresponding hydroxy derivatives together with the corresponding fluoro derivatives. The amount of hydroxy compounds can be reduced if the concentration of tetrafluoroborate ions in the medium is increased (75MI1).

4. *Diazoindazoles*

Flash vacuum thermolysis of 6-chloro-3-diazoindazole (**2b**) resulted, upon loss of nitrogen, in the formation of carbene **102**, which could intramolecularly rearrange to the nitrene **103**, or to the azabenzocyclopropene **104**, or to azacycloheptatrienyliene **105** (Scheme 29). The only isolable product was **106**, formed by dimerization of the nitrene **103** (78CB2258).

All the 3-diazoindazoles **2**, irradiated in an aromatic solvent (benzene, *p*-chlorotoluene, benzonitrile, 1,2-dimethoxybenzene), gave by ring substitution the corresponding 3-arylindazoles in variable yields (66LA17). 3-Diazoindazole **2b**, irradiated in pyridine and in thiophene, gave the 6-chloro-3-(2-pyridyl)-indazole and the 6-chloro-3-(2- or 3-thiophenyl)-indazole (66LA17).

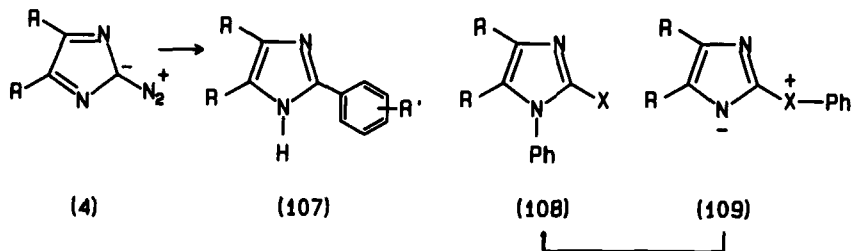
Photolysis of 3-diazoindazole **2b** in cyclohexane resulted in formation of the azoderivative **106** (78CB2258). 3-Diazoindazoles **2a,c,d**, irradiated in alcohols (methanol, ethanol, or isopropanol, gave by reductive diazo cleavage the corresponding indazoles together with the carbonyl compounds (66LA17; 74JOC1833; 76T725).



SCHEME 29

5. Diazoimidazoles

a. *2-Diazoimidazoles*. Thermolysis and photolysis of 2-diazoimidazoles **4** in benzene derivatives led to 2-arylimidazoles **107** [73JA2695; 79JOC1717; 80DIS(B)(40)3747] (Scheme 30). No ring-expansion product was isolated even when the reaction was carried out in presence of cuprous salts known to favor the ring expansion of benzenes in the reaction with diazo compounds (78MI4). Thermolysis of **4** (R = CN) in trifluoromethylbenzene also gave 1- α,α -difluoromethyltoluene-2-fluoroimidazole derived from insertion into a C—F bond (73JA2695). Reaction of **4** in halo-benzenes led to, aside from product **107**, compounds **108** by 1,2 insertion of the intermediate carbene into the C—X bond. The reaction also led to **109**, the halonium ylide that on heating rearranged to compound **108**. The yields of **109** varied according to the stability of the halonium ylide, and in the



SCHEME 30

TABLE IX
 PRODUCTS (YIELD %) OF 2-DIAZOIMIDAZOLE WITH MONOSUBSTITUTED BENZENES ^a

R'	Reaction condition ^b	<i>o</i>	107 <i>m</i>	<i>p</i>	Reaction with R'
OMe	P	25	—	24	10 ^c
N(Me) ₂	P	43	—	23	—
CH(Me) ₂	P	31	—	26	—
H	T/P	73/68	73/68	73/68	—
F	P	44	—	29	—
Br	P	18	—	19	12 ^d
I	T/P	11/7	—	24/9	4/8 ^e
CN	P	> 15	—	> 31	—
NO ₂	T/P	—	—	7	> 90/82
COMe	T/P	—	11	—	—
CO ₂ Me	T/P	—	54/56	—	—
CF ₃	P	—	> 86	—	—

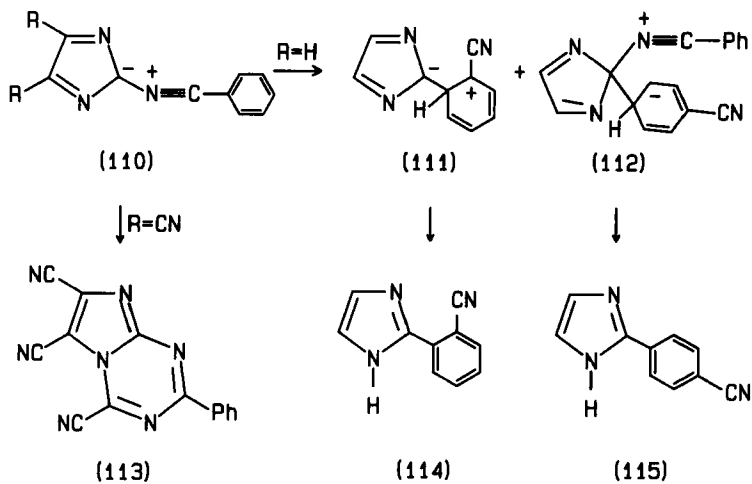
^a Reference, 80DIS(B)(40)3747.^b T, Thermolysis; P, photolysis.^c 2-phenoxyimidazole.^d 2-bromo-1-phenylimidazole.^e phenyliodonium-imidazolylide.

case of fluorobenzene, the ylide was not formed [73JA2695; 80DIS(B)(40)3747] (Table IX).

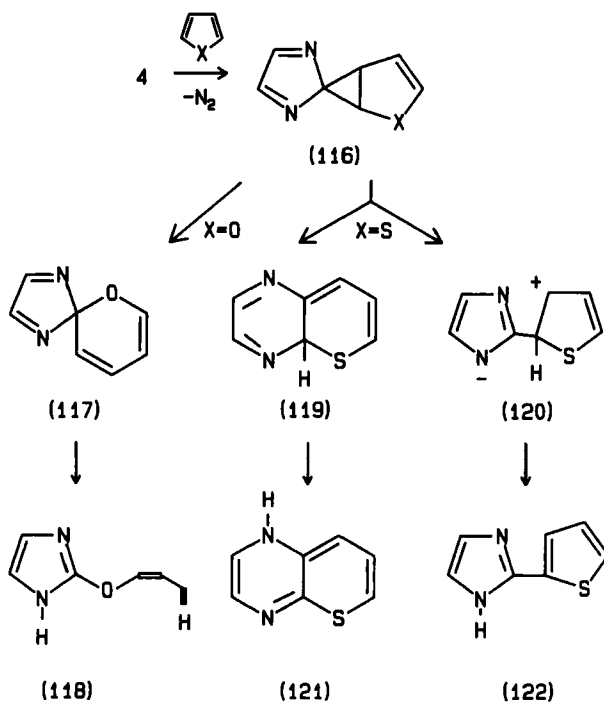
The formation of the ylides **110** (Scheme 31) was invoked to explain the anomalous ortho-para directing power of the cyano group. Compound **110** (R = H) can either rearrange to intermediate **111** or undergo nucleophilic substitution on the para position of another molecule of benzonitrile to give the adduct **112**. Structure **111** leads to the ortho-substitution product **114**, while intermediate **112** gives rise to the para-substitution product **115** [80DIS(B)(40)3747]. Ylide **110** (R = CN), because of the electron-withdrawing power of the cyano groups, adds to another molecule of benzonitrile to give **113** (79JOC1717).

The same ortho-para directing power was also observed with the nitro group, but the main product of this reaction was the nitrosobenzene that originated from a deoxygenation process [80DIS(B)(40)3747]. Another reaction with the substituent was observed with anisole; in this case, the ether scission took place to give the 2-phenoxyimidazole [80DIS(B)(40)3747] at variance with the pyrazole series where the ether cleavage led to *N*-methylated structures (77JA633).

In the photolysis with heteroaromatic derivatives, 2-diazoimidazole (**4**) (R = H) (Scheme 32) behaves in different ways depending on the



SCHEME 31

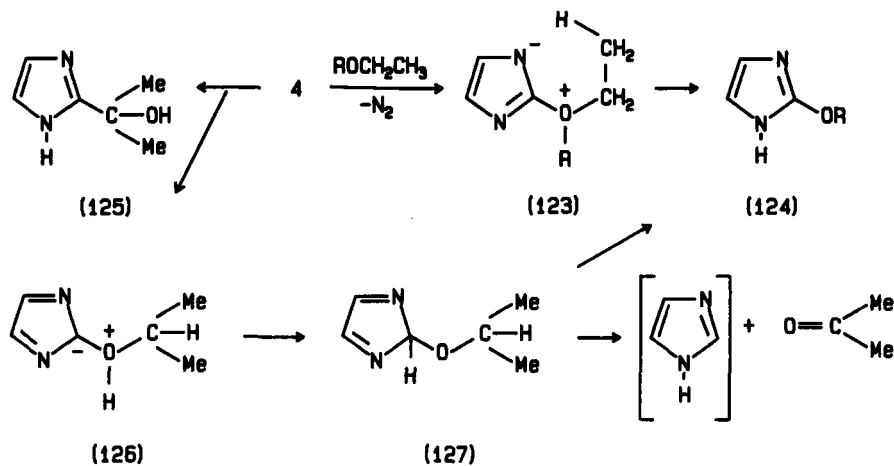


SCHEME 32

nature and size of the heterocycle. With pyridine derivatives, the behavior is analogous to that observed in benzene series, leading, with the same mechanism, to the corresponding ring substitution products [80DIS(B)(40)3747]. On the contrary, with five-membered heterocycles, furan and thiophene products derived from ring opening and ring enlargement were also obtained [80DIS(B)(40)3747]. Thus, photolysis in furan gave the ether **118**, which was apparently formed by electrophilic attack of the intermediate carbene on the oxygen, followed by ring cleavage. The furan highest occupied molecular orbital (HOMO) has no electron density on the oxygen, but it does have suitable symmetry for the empty π orbital of singlet carbene for addition to the double bond of furan. The pathway to **118** may involve formation of spirocyclopropane **116** that ring-expands to the spiro intermediate **117**. 1,2-Elimination about the 4–5 double bond of the pyran ring and proton migration lead to **118**. Photolysis in thiophene led to equal amounts of compounds **121** and **122**. The formation of the two compounds could go through the same intermediate **116**. Heterolytic rupture of the cyclopropane ring, through the intermediate **120**, gives **122**; ring enlargement of **116** leads to **119**, which rearranges to **121**.

Thermolysis and/or photolysis of **4** in aliphatic halides resulted in the formation of the corresponding 1,2-addition products (73JA2695). Photolysis in cyclohexene gave the 2-cyclohexenylimidazole by allylic insertion, whereas insubstituted butenes it led to no isolable products [80DIS(B)(40)3747].

Photolysis of 2-diazoimidazole **4** in diethyl and vinyl ether led to the corresponding alkoxy derivatives **124** (R = ethyl, vinyl) (Scheme 33). The

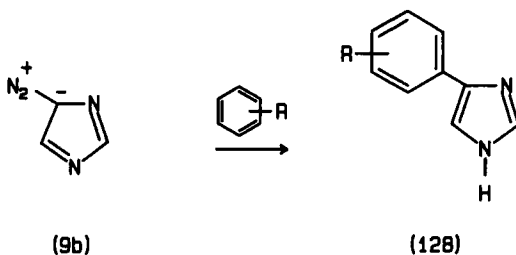


SCHEME 33

mechanism involves the attack of the oxygen on the intermediate carbene to give the oxonium ylide **123**, which eliminates ethylene [80DIS(B)(40)3747].

Photolysis of **4** in 2-propanol led to the corresponding ether **124** (R = isopropyl), acetone, and a small amount of the alcohol **125**. While the formation of the alcohol is explained via C—H insertion into isopropanol by singlet carbene, the mechanism leading to the ether **124** is not clear. Probably the 2-propanol attacks the carbene to give the ylide **126**, which by rearrangement gives **127** and then **124**. To explain the formation of acetone and of imidazole, which, incidentally, could not be detected in the reaction environment, several mechanisms were proposed [80DIS(B)(40)3747]. In our opinion, however, involvement of the same intermediate **127**, which disproportionates to acetone and imidazole, can be invoked. Support for this mechanism is given by similar behavior observed in the indole series where isolated 3-alkoxy derivatives **76c,d** disproportionated upon photolysis to the parent indoles (**76e,f**) and carbonyl compound (75CB3326) (see Scheme 21). However, contrary to expectation, the thermolysis of 2-diazoimidazole **4** (R = CN) in ethanol only gave the redox reaction, leading to 4,5-dicyanoimidazole and acetaldehyde (73JA2695). Because of the presence of the electrophilic cyano groups, the diazo abstracts a hydride ion from the ethanol or first adds ethanol.

b. *4-Diazoimidazoles*. Photolysis and thermolysis of 4-diazoimidazole **9b** in benzene derivatives led exclusively to 4-arylimidazoles **128** as products of ring substitution; the formation of ring-expansion products was not observed (86TL901) (Scheme 34). For **9b**, anomalous behavior was observed in substituents having lone pairs on atoms bonded to the group. Thus, with anisole, 4-phenoxyimidazole was produced by ether cleavage. With cyano and nitro groups, a relatively large amount of ortho substitution was obtained because of the intermediacy of ylide analogues of **110**. With chlorobenzene, a secondary process is the decomposition of the intermediate ylide analogue of **109** either to 4-chloroimidazole, by



SCHEME 34

homolytic decomposition, or to 1-phenyl-4-chloroimidazole by isomerization (86TL901) (Table X).

Photosensitized decomposition of **9b** in substituted benzenes led to similar results [83DIS(B)(44)1113]. Therefore, either spin inversion from the triplet to the singlet form of 4-diazoimidazole is faster than the decomposition of the excited diazo compound, or intersystem crossing from the triplet to singlet carbene is easier and faster than the reaction of the triplet state with substrates.

The phototransformations of 4-diazoimidazole-5-carboxamide (**9a**) (Scheme 35), extensively studied because of their biological interest (see Section V,B), are markedly influenced by the pH values in dilute aqueous solution [81JCS(P1)1433]. At pH 1, or in the pH range 7.4–12, the diazo compound cyclized exclusively to 2-azahypoxanthine (**131**). In weak acid, the product was the imidazolium-olate **132** ($R = H$). The proposed mechanism for the photochemical reaction in the pH range 1–7.4 involves the formation of the intermediate carbene species **10**, heterolytic S_N2 or S_N1 displacement by water or a homolytic process being less probable. Regarding the formation of **131** at pH 1, the reactive species is the diazonium salt **129**, whereas the intermediate formation of a diazohydroxide derivative **130** is invoked at pH 7.4 and above. In concentrate aqueous solution (at pH 2.5), the maroon colored product **132** [$R = \text{azo-(5-carboxamidoimidazol-4-yl)}$] was formed upon photolysis, together with **131**. In the case of preparative scale photolysis, the deeply colored dye sheltered the solution from the light so that in the dark, the hypoxanthine derivative **131** was

TABLE X
PRODUCTS (YIELD %) OF 4-DIAZOIMIDAZOLE WITH MONOSUBSTITUTED BENZENES^a

R	Reaction condition ^b	<i>o</i>	128 <i>m</i>	<i>p</i>	Reaction with R
OMe	T/P	67/57	—	20/28	13/14 ^c
C(Me) ₃	T/P	61/61	—	27/29	10 ^d
Cl	T/P	11/>1	—	71/80	18 ^e
H	T/P	38/46	38/46	38/46	—
CF ₃	T/P	12/16	88/84	—	—
CN	T/P	45/49	55/51	—	—
NO ₂	T/P	68/61	32/27	-/11	—

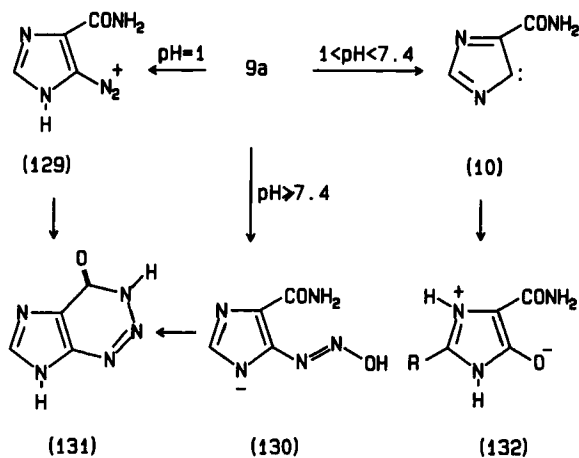
^a References, 83DIS(B)(44)1113; 86TL901.

^b T, Thermolysis; P, photolysis.

^c 4(5)-Phenoxyimidazole.

^d 4(5)-(2-Methyl-2-phenylpropyl)imidazole.

^e 4(5)-Chloroimidazole (15%) and 5-chloro-1-phenylimidazole (> 3%).

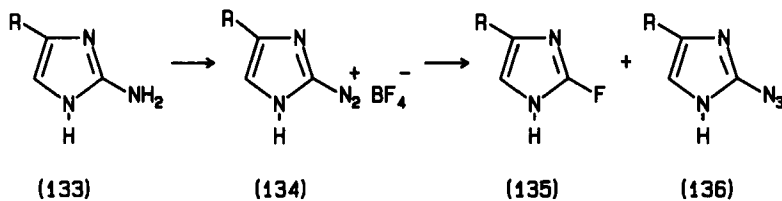


SCHEME 35

formed. In fact, in the dark, only 2-azahypoxanthine was formed in the pH range 1–12; the rate of cyclization accelerated as the pH increased.

c. *Imidazole Diazonium Salts.* Photolysis of a solution of imidazole-2-diazonium tetrafluoroborates of type **134**, generated in situ by diazotization in tetrafluoroboric acid of the corresponding 2-aminoimidazoles **133**, led to 2-fluoroimidazoles **135** and occasionally to traces of 2-azidoimidazoles **136**, which became the sole product in the thermolysis when $R = H$ (71JA3060; 73JA8389) (Scheme 36). In this same way, 2,4-difluoroimidazoles were obtained upon photolysis of 4-fluoroimidazole-2-diazonium salts (84JOC1951). 2-Fluorobenzimidazole was also prepared (75MI1).

Imidazole-4-diazonium tetrafluoroborate also showed similar reactivity upon photolysis and led to the corresponding 4-fluoro derivatives (71JA3060). When the 4-aminoimidazoles are too unstable to be isolated, it



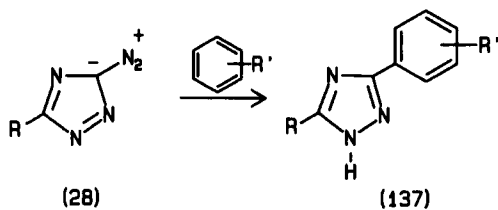
SCHEME 36

is possible to carry out a one-pot reaction from the nitro to the fluoro derivatives by reduction, diazotization in tetrafluoroboric acid, and photolysis of the resulting solution (73JOC3647). Only in the case of the 5-carboxamidoimidazole-4-diazonium salt was the fluoro derivative not obtained because cyclization to 2-azahypoxanthine was faster than photo-fluorination (73JA4619).

6. Diazotriazoles

a. *3-Diazo-1,2,4-triazoles*. Flash vacuum pyrolysis of 5-phenyl-3-diazo-1,2,4-triazole caused decomposition to benzonitrile [81DIS(B)(42)1892]. Thermolysis and photolysis of 3-diazo-1,2,4-triazoles **28** in benzene derivatives gave the corresponding 3-aryl-1,2,4-triazoles **137** (Scheme 37); ring-expansion products were not obtained [1898LA33; 81DIS(B)(42)1892; 86DIS(B)(46)3052] (Table XI).

With strong electron-withdrawing groups, ylidic coordination did not take place in this series, and meta substitution was observed exclusively. Pyridine gave substitution in its meta position since the ring nitrogen behaves as an electron-withdrawing substituent; a minor process is the formation of an isolable ylide [81DIS(B)(42)1892]. In the unsubstituted diazotriazole **28** ($R = H$), the yield of ortho products increased with increasing temperature. The increased selectivity at higher temperatures is very unusual. Generally in electrophilic aromatic substitution, the reaction with varied benzenes becomes less selective as the temperature increases. Such a behavior can be justified considering that **139**, an electrophile and therefore a Lewis acid (Scheme 38), is highly solvated by substituted benzenes. Thus, the transition states resembling norcaradienes do not sense the effect of the substituent in a monosubstituted benzene undergoing addition because of the presence and the organization of the solvent. At higher temperatures, the carbene will be less solvated. Thus, relatively naked **139** can attack the aromatic ring of a substituted benzene and make greater relative use of substituent effects, particularly at the ortho po-



SCHEME 37

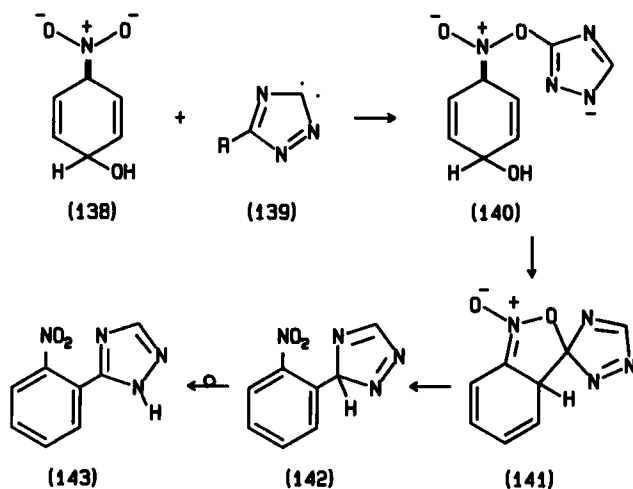
TABLE XI
 PRODUCTS OF 3-DIAZO-1,2,4-TRIAZOLES IN MONOSUBSTITUTED BENZENES^a

28 R	Benzene R'	Reaction condition ^j	Relative percentages of 137			Yield ^k	with R'
			<i>o</i>	<i>m</i>	<i>p</i>		
H	OMe	T/P	67/53	11/10	22/37	NR/28	—
H	Me	T/P	68/59	11/10	21/31	NR/NR	—
H	H	T/P	—	—	—	36/47	—
H	CH(Me) ₂	T/P	6/14	39/35	54/51	NR/NR	—
H	F	T/P	55/60	15/12	30/28	NR/NR	—
H	Cl	T/P	74/76	8/8	18/16	63/NR	—
H	Br	T/P	58/63	58/63	42/37	NR/NR	—
H	CN	T/P	2/20	96/62	2/18	NR/NR	—
H	CF ₃	T/P	84/83	84/83	16/17	NR/NR	—
H	CO ₂ Me	T/P	39/53	61/47	—	NR/NR	—
H	NO ₂	T	—	100	—	25	42
Ph	OMe	T/P	42/50	—	58/50	48/50	—
Ph	CH(Me) ₂	T/P	51/50	—	49/50	47 ^b	13/14 ^c
Ph	Me	T/P	67/53	—	33/47	79/70	12/9 ^d
Ph	H	T/P	—	—	—	77/83	—
Ph	Cl	T/P	9/34	—	91/66	44/53	Tr ^e
Ph	Br	T/P	55/30	—	45/70	47/52	14/21 ^f
Ph	I	T/P	—	—	—	—	57/76 ^g
Ph	CN	T/P	—	100	—	52/50	—
Ph	CF ₃	T/P	—	100	—	68/59	6/7 ^h
Ph	NO ₂	T/P	—	100	—	17/17	77/45 ⁱ

^a References, 81DIS(B)(42)1892; 86DIS(B)(46)3052.^b The two compounds were not separated.^c 3-[1-(Phenylpropyl)]-5-phenyl-1,2,4-triazole.^d 3-Benzyl-5-phenyl-1,2,4-triazole.^e 5-Chloro-1,3-diphenyl-1,2,4-triazole.^f 5-Bromo-1,3-diphenyl-1,2,4-triazole.^g Two products were isolated: 5-Iodo-1,3-diphenyl-1,2,4-triazole (47/39%) and 3-iodo-5-phenyl-1,2,4-triazole (10/37%).^h 5-Fluoro-1-(α,α -difluorobenzyl)-3-phenyl-1,2,4-triazole.ⁱ Nitrosobenzene.^j T, Thermolysis; P, photolysis.^k NR, Yield not reported.

sition. Anomalous behavior of 28 (R = Ph) was observed with halobenzenes. Thus, with iodobenzene, 3-iodo-5-phenyl-1,2,4-triazole and 1,5-diphenyl-3-iodo-1,2,4-triazole were isolated without any substitution product [81DIS(B)(42)1892].

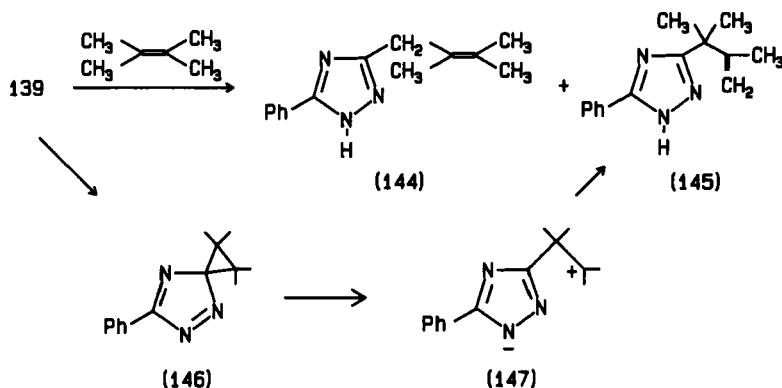
3-Diazotriazole 28 (R = Ph), upon thermolysis or photolysis in nitrobenzene or other nitro compounds, showed only oxygen abstraction to



SCHEME 38

give nitroso compounds and benzonitrile, which are derived from the decomposition of 5-phenyl-1,2,4-triazol-3-one together with nitrogen and carbon monoxide [81DIS(B)(42)1892]. This type of reactivity can be widely used as a method for the selective reduction of nitro-to-nitroso group in yields ranging from good to excellent. In the case of **28** ($R = H$) in anhydrous nitrobenzene, together with a deoxygenation process that gave nitrosobenzene, the ring-substitution process leading to the meta substitution product was observed [86DIS(B)(46)3052]. The behavior of **28** ($R = H$), upon thermolysis or photolysis in basic, aqueous nitrobenzene, differs from that observed in anhydrous nitrobenzene. Thus, **28** did not undergo deoxygenation and mainly gave the product formed by ortho substitution. Triazolyldiene **139** reacts with the adduct **138**, obtained by reaction of sodium hydroxide with nitrobenzene, to give **140** by coordination of the carbene with the oxygen of the nitronate group. Nucleophilic attack of the triazole moiety on an ortho benzenoid position gives **141**. This spiran undergoes rapid base-catalyzed conversion to **142**, which rearanges to **143**. In this way the formation of spironorcaradienes leading to meta substitution is limited.

Thermolysis and photolysis of **28** ($R = Ph$) in cyclohexene gave a mixture of 3(2-, 3-, 4-cyclohexenyl)-5-phenyl-1,2,4-triazole [81DIS(B)(42)1892]. Thermal decomposition in 2,3-dimethyl-2-butene gave a mixture of **144** and **145** [81DIS(B)(42)1892] (Scheme 39). Compound **145** might arise from attack of the carbene **139** ($R = Ph$) on the double bond of the 2,3-dimethyl-2-butene to give an intermediate cyclopropane

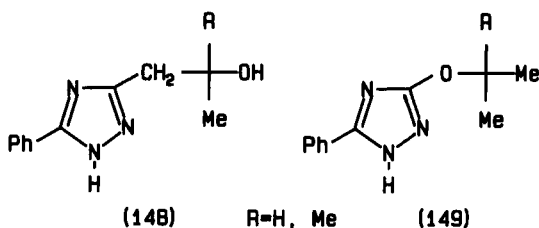


SCHEME 39

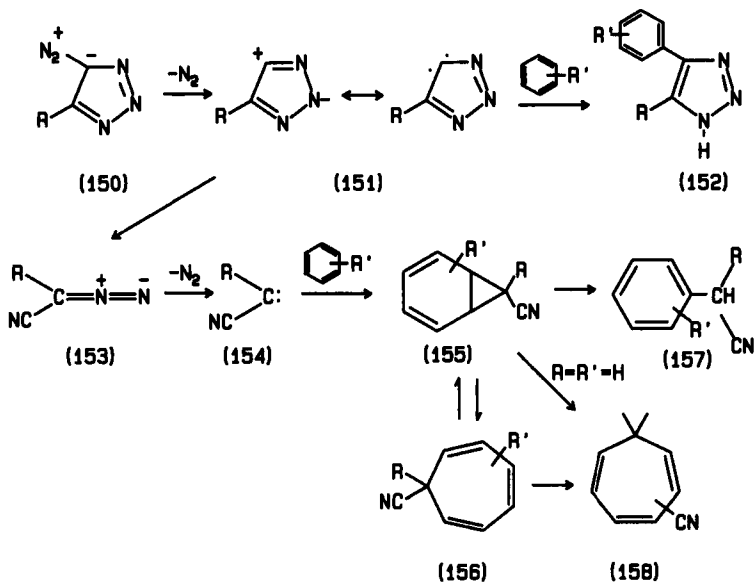
146 that heterolytically cleaves to zwitterion **147** which, upon proton transfer, gives **145**.

3-Diazotriazole **28** ($R = \text{Ph}$) reacted with *t*-butyl alcohol and 2-propanol to give compounds **148** and **149** (Scheme 40) in comparable yields by carbenic C—H insertion and nucleophilic substitution, respectively [81DIS(B)(42)1892]. In the case of 2-propanol, an oxidation–reduction process, to give the parent triazole and acetone, was also observed to a smaller extent. Also, it was previously reported that 3-diazotriazole **28** ($R = \text{COOH}$) oxidizes primary and secondary alcohols to the corresponding aldehydes and ketones (1898LA33).

b. *4-Diazo-1,2,3-triazoles*. Thermolysis and photolysis of diazotriazoles **150** (Scheme 41) gave complex mixtures in which all the components were occasionally impossible to isolate and identify. [83DIS(B)(43)2557]. Thermal or photolytic decomposition of the diazo compounds led to the corresponding triazolyldenes **151**. The carbenes can undergo two different competing processes. The main process involves the ring scission to



SCHEME 40



SCHEME 41

diazoacetone nitriles **153** that, upon loss of nitrogen, generate cyanocarbenes **154**. Adding **154** to benzenes yields cyanonorcaradienes **155** that exist in equilibrium with their valence tautomer **156**. Such an equilibrium is shifted toward **155** when R' is an electron-withdrawing group. Compound **155** can also undergo ring expansion to compound **158** or aromatize to **157** (Table XII).

A correlation between the electronic effects in the benzenes and the selectivity and reactivity of the carbenes was not observed. Photolysis and thermolysis did not give uniformity in product distribution. In the thermolysis, normally more aromatic substitution was observed, whereas in the photolysis more product derived from ring scission of the triazolylenes was obtained. These findings may be explained in terms of the more excited carbene generated by photolysis, which makes the ring scission easier and has too short a lifetime to be trapped by the solvent. In the thermolysis, the solvent has more chances to catch the carbene both because of the longer lifetime and the increased solubility of the diazo compound at an elevated temperature. The longer lifetime also allows the intersystem crossing to triplet carbene which, upon hydrogen abstraction, gives rise to reduction product **152** ($R = R' = H$). Oxygen abstraction was also observed in the photolysis of **150** in nitrobenzene with formation of nitroso benzene [83DIS(B)(43)2557].

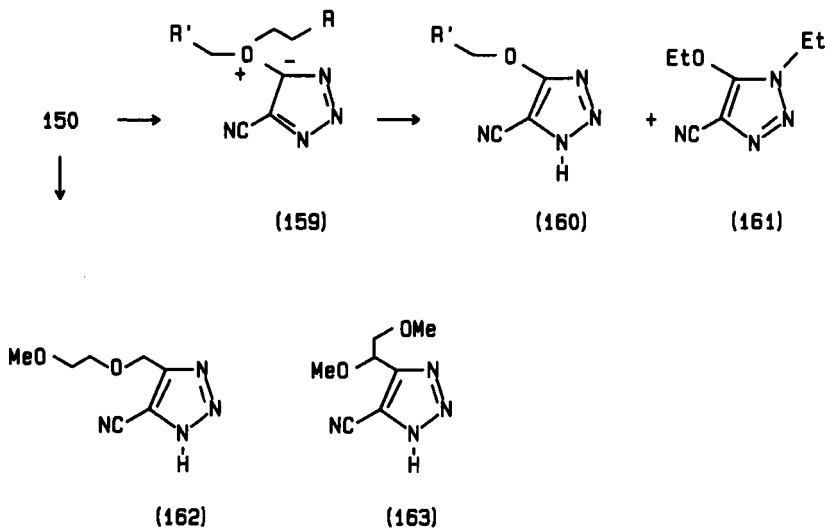
TABLE XII
 PRODUCTS (YIELD %) OF 4-DIAZO-1,2,3-TRIAZOLES IN SUBSTITUTED BENZENES^a

150 R	Benzene R'	Reaction condition ^b	<i>o</i>	152 <i>m</i>	<i>p</i>	155	156	157	158	Others
H	H	T/P	48/26	48/26	48/26	—	—	—	18/54	—
Ph	H	T/P	28/16	28/16	28/16	—/38	—	—	—	11 ^c /30 ^d
H	Me	P	—	—	—	10	57	—	—	—
H	1,4-diMe	P	—	—	—	17	17	—	—	—
H	CF ₃	P	—	—	—	46	19	—	—	—
H	Br	P	—	—	—	43	11	—	—	—
H	F	P	—	—	—	18	18	—	—	—
H	NO ₂	P	—	42	—	8	—	—	—	18 ^e
Ph	NO ₂	P	—	17	—	—	—	—	—	45 ^e
Ph	Me	T/P	—	—	24/8	54/17 ^f	—	—	—	6 ^g /33 ^h
CO ₂ Et	H	P	—	—	—	23	—	58	—	—
CN	H	P	—	—	—	28	—	43	—	—
CN	OMe	T	28	—	21	—	—	—	—	12 ⁱ

^a Reference, 83DIS(B)(43)2557.^b T, Thermolysis; P, photolysis.^c 4-Phenyl-1,2,3-triazole (11%) and four other unidentified products.^d Benzoyl cyanide azine (5%); 9,10-dicyano-9,10-dihydrophenanthrene (8%); 9,10-dicyanophenanthrene (11%); and an unidentified product (6%).^e Nitrosobenzene.^f Mixture of three isomers.^g 4-Phenyl-1,2,3-triazole.^h Unidentified product.ⁱ 4-Cyano-5-phenoxy-1,2,3-triazole.

4-Diazotriazole **150** (R = CN) reacted with diethyl ether to give the addition product **160** (R' = Me) together with the 1,2-addition product **161** [83DIS(B)(43)2557] (Scheme 42). The intermediate ylide **159**, formed either by addition of the ether to the triazolylidene **151** or to the diazo **150** and subsequent loss of nitrogen, underwent elimination of alkene to give **160** or displacement on carbon next to the oxygen to yield **161**. In the reaction with 1,2-dimethoxyethane, compounds **160** (R' = H), **162** and **163** were obtained in comparable yields by inserting the triazolylidene into the primary or secondary CH bonds of the ether [83DIS(B)(43)2557].

In the reaction with 2-propanol, 4-diazotriazole **150** (R = Ph) showed a behavior similar to the 2-diazo-4,5-dicyanoimidazole, in that 4-phenyl-1,2,3-triazole and acetone were obtained [83DIS(B)(43)2557]. For this reaction, two different mechanisms were proposed, but in both, the first step is the addition of the highly nucleophilic diazotriazole to the alcohol.

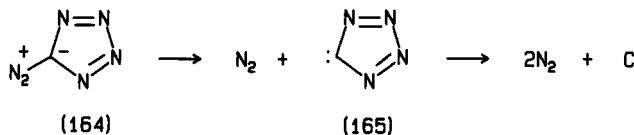


SCHEME 42

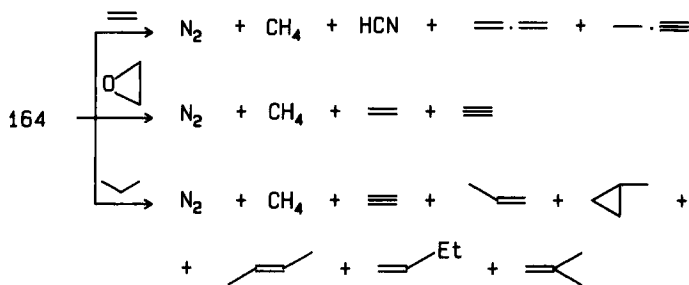
7. Diazotetrazole

Thermal decomposition of diazotetrazole **164** produced carbon and nitrogen probably via the unstable tetrazolylidene **165** (Scheme 43). Thus, the reactions of carbon atoms are suitably studied by coating the walls of a flask with the diazo compound and thermally decomposing it in the presence of a gaseous reactant. When **164** was decomposed in an atmosphere of carbon monoxide, the major product was carbon suboxide, likely produced through the initial formation of C_2O which adds a molecule of carbon monoxide to generate C_3O_2 (73JA4441).

Decomposition of **164** in ethylene, ethylene oxide, and propane mainly gave C—H insertion and hydrogen abstraction products by carbon atoms (72JA1379; 77JA2627) (Scheme 44). In ethylene oxide, oxygen abstraction was also observed.



SCHEME 43

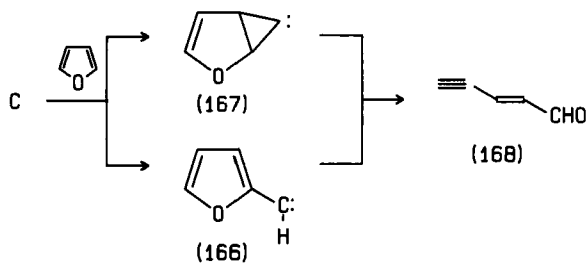


SCHEME 44

Pyrolysis of diazotetrazole (**164**) generated atomic carbon that, in the presence of gaseous furan, gave the unsaturated aldehyde **168** (Scheme 45) as the major volatile organic compound (79JA1303). The formation of **168** can be rationalized either by C—H insertion of the carbon atoms to generate **166**, which then rearranges, or by addition of carbon to one of the double bonds of furan to give a cyclopropylidene intermediate **167**, which by ring opening leads to **168**. The use of ^{13}C -labeled diazocompound demonstrated that only a small amount of **168** is originated by C—H insertion; **168** mainly results from the addition to the double bond followed by ring opening.

B. REACTION WITH ELECTROPHILES

The only reactions of diazoazoles with electrophiles are those with acids. The reaction with acids at room temperature or below has already been reviewed in the section on diazo-diazonium equilibrium. This section includes reported reactions occurring at higher temperatures which generally resulted in decomposition and/or self-coupling reactions.



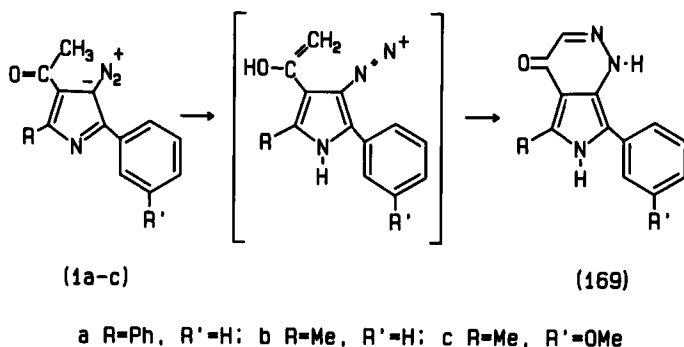
SCHEME 45

Diazoazoles are usually resistant to oxidizing agents [06G56; 60CI(L)659], except that the diazopyrroles are extensively decomposed by strong oxidants (23G795).

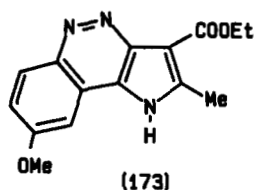
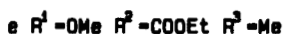
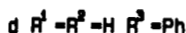
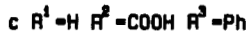
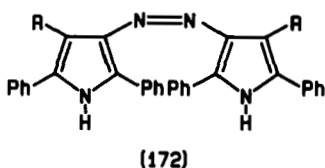
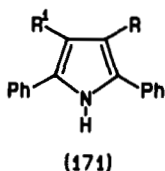
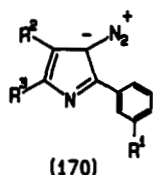
1. Diazopyrroles

4-Acetyl-3-diazo-2-phenyl-5-substituted pyrroles **1** in diluted sulfuric acid (25%) or acetic acid led to the pyrrolo[3,4-*c*]pyridazine ring system **169** by an intramolecular coupling reaction of the diazonium group with the enolic form of the acetyl group (Scheme 46). The acid catalysis was necessary since the pyrrolo-pyridazines were not obtained in refluxing pentanol or in dimethylformamide (DMF) [83H(20)255]. In these reactions, 3-diazopyrroles always showed a preferential reactivity towards the substituent in the 4-position of the nucleus. In fact, the coupling reaction with the phenyl in the 2-position, in acid conditions, did not take place even when the 4-position bore groups unreactive towards the diazonium group.

These diazo compounds behaved like aromatic diazonium salts, giving intermolecular coupling reaction and decomposition products [83H(20)829]. Thus, 3-diazo-2,5-diphenyl-4-substituted pyrroles **170a,b** gave the parent pyrroles **171a,b**, 3,3'-azobispyrroles **172** ($R = H, CN$; these were formed by intermolecular coupling between the diazonium group and the pyrrole formed by decomposition of the starting material), and the diazo compounds **170c,d** upon hydrolysis and decarboxylation of the 4-substituents (Scheme 47). In acetic acid, only compounds **171c,d** were isolated. The coupling with the 2-phenyl only took place when there was no competition with the 4-position and an activating group, such as a methoxy group, was present in the suitable position of the phenyl ring



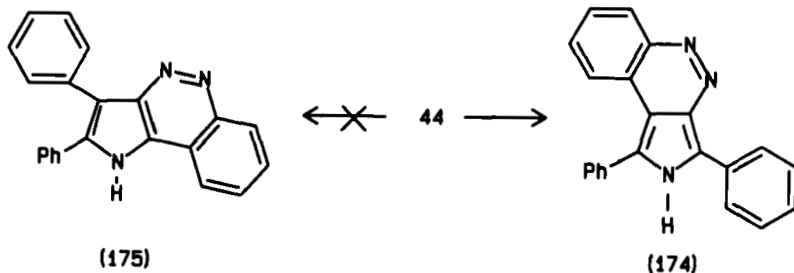
SCHEME 46



SCHEME 47

[84H(22)2269]. In fact, compound **170e** coupled with the activated phenyl to give the pyrrolo[3,2-*c*]cinnoline **173**, while compound **1c** still coupled with the 4-position to give the pyrrolo-pyridazine **169c**.

In the same way, 3-diazo-2,4,5-triphenylpyrrole (**44**) did not show any reactivity towards the phenyl in the 2-position. Thus **44**, refluxed in diluted sulfuric acid (25%) for 36 hrs, gave the pyrrolo[3,4-*c*]cinnoline ring system **174** by an intramolecular coupling reaction with the phenyl in the 4-position (09G134) (Scheme 48). The coupling reaction could take place either on the phenyl in the 4- or 2-positions to give, respectively, pyrrolo[3,4-*c*]cinnoline **174** or pyrrolo[3,2-*c*]cinnoline **175**. The structure was then assigned considering that, under the same reaction conditions, 3-diazo-2-phenylindole did not couple with the phenyl in the 2-position to give indolo[3,2-*c*]cinnoline (06G56).



SCHEME 48

The structure of compound **174** was shown to be correct 60 years later by an independent synthesis of 3,4-dibenzoylcinnoline, an oxidation product of the pyrrolo[3,4-*c*]cinnoline obtained by action of nitric acid [69JCS(C)1795]. The coupling reaction with the phenyl in the 2-position was observed only in 1-substituted pyrrole diazonium compounds, probably because the phenyl on the nitrogen does not allow the coplanarity of the pyrrole and benzene rings, avoiding the hyper-ortho effect of the diazonium group which makes the ring unreactive as happens when the pyrrole nitrogen is unsubstituted [54MI1; 60AC(R)237].

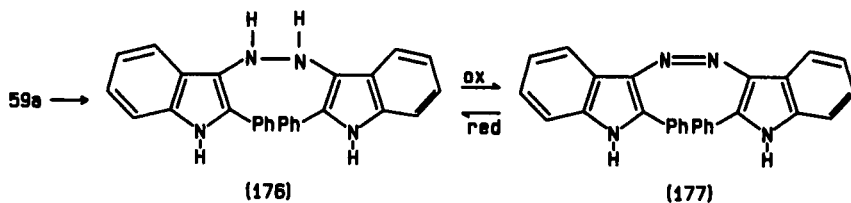
2. Diazoindoles

3-Diazo-2-phenylindole (**59a**) remained unchanged upon reaction in concentrated sulfuric acid, whereas dilute sulfuric acid gave the hydrazo compound **176** (37G633) (Scheme 49). The azo structure **177** was previously assigned to the product of this reaction (06G56). However, the true structure **176** was confirmed by oxidation to **177** with amyl nitrite. Compound **177** in turn gave back the hydrazo compound by reduction with ammonium sulfide (37G710). Moreover, the same compound **177** was obtained by independent routes [66JCS(C)1345; 66LA17] (see Sections III,C,2 and IV,B,2).

Compound **21d** reacted with bromine in carbon tetrachloride to give **76g** in high yield, probably by electrophilic displacement of nitrogen and subsequent combination of the bromide with the carbocation (64JOC3577).

3. Diazopyrazoles

5-Benzoyl-3-diazo-4-phenylpyrazole, decomposed in hot sulfuric acid (50%) with evolution of nitrogen but no pure product, could be isolated [60CI(L)659]. By contrast, 4-diazopyrazoles were very stable in strong acids [60CI(L)659], especially the unconventional diazo **22a** in which, due to the particular mesomeric structure, protonation at the ipso carbon is not



SCHEME 49

possible [78H(10)199]. 4-Diazopyrazoles **87** in acetic acid led to pyrazolo-pyrazole derivatives **88** ($R' = H, Ph$) by an intramolecular coupling reaction with the methylene in the ortho position (62JA1399; 73TL1199) (see Scheme 26). A radical chain pathway was invoked for this transformation [60CI(L)659], one that can also occur in different acids (*n*-butenoic or benzoic). In the case of **87** ($R' = H$), if acetic anhydride is present, some or all the iminic groups were acetylated depending on the solvent, temperature, and molar ratio of the reagents (74YZ17); the formation of an intermediate diazonium acetate was proposed.

4. Diazoimidazoles

2-Diazo-4,5-dicyanoimidazole in acetic acid decomposed to the corresponding imidazole, but in hot water or aqueous acetic acid it gave quantitative evolution of nitrogen and intractable tars (79JOC1717). 4-Diazoimidazole-5-carboxamide treated with 30% sulfuric acid at 95°C in the presence of copper bronze did not give the hydroxy compound, but cyclized to 2-azahypoxanthine, the same compound obtained by thermolysis and photolysis in acid [81JCS(P1)1433].

C. REACTION WITH NUCLEOPHILES

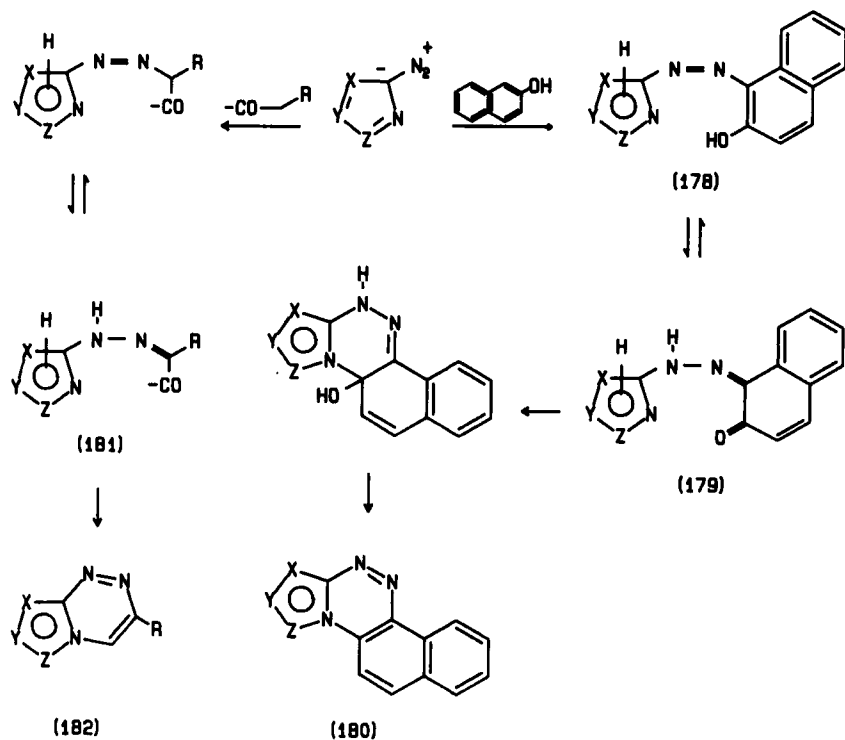
Among the reactions of diazoazoles, the reaction with nucleophiles is the most useful for synthetic purposes. A great variety of derivatives can be prepared depending on the diazo component and on the coupling agent as verified by over 130 reports dealing with this topic. Generally both the diazoazole and its conjugate acid are capable of coupling although the diazo form is much less reactive. The azole-diazonium salts show the expected reactivity of aromatic diazonium salts, whereas some of the diazo forms are not sufficiently electrophilic to undergo coupling with even the most reactive nucleophiles. This lack of reactivity is observed in all the diazoazoles in which there is not a nitrogen adjacent to the reactive center, i.e., 3-diazopyrroles, 3-diazoindoles, and 4-diazopyrazoles. In these cases, it is necessary to first generate the diazonium species by an acid-base interaction where the role of acid can even be played by the coupling agent. Among the reactive diazo species, azasubstitution enhances reactivity. The nature of the heterocycle also affects the evolution of the primary coupling products. Thus, for example, in the coupling reactions of diazoazoles with β -naphthol, the azocompounds **178**, which also exist in tautomeric equilibrium with the hydrazo form **179**, can cyclize to naphthoazolo-triazine **180**. The cyclization rate depends on

the relative basic character of the heterocycle and decreases in the order imidazole \gg pyrazole $>$ 1,2,4-triazole $>$ 1,2,3-triazole $>$ tetrazole (74JHC867) (Scheme 50).

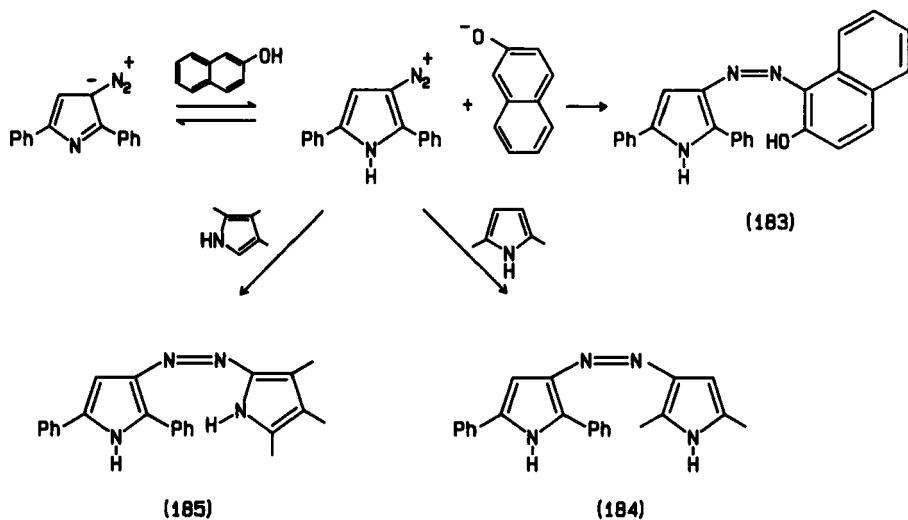
In analogous fashion, the basicity of the azole ring affects the ring closure to azolo-triazines **182** of the hydrazones **181** obtained from the coupling reaction of diazoazoles and methylene active compounds (76JMC517).

1. Diazopyrroles

2-Diazopyrroles readily coupled with β -naphthol to give azo dyes (62JCS1638), whereas the coupling reaction of 3-diazopyrroles with phenols did not take place under standard conditions since in neutral or alkaline media they precipitated. The reaction did occur if the diazo compounds were added to fused β -naphthol or in aprotic organic solvents (60JCS3270). Probably, a base-acid reaction leading to an equilibrium



SCHEME 50



SCHEME 51

between the starting species and diazonium compound plus β -naphthoxide took place. The ionized species, even if formed to a small extent, rapidly couple to give the azo compound **183** (Scheme 51). It is likely that in aqueous or protic solvents, the solvation of the species does not allow the base-acid interaction that seems to be necessary to bring about the coupling reaction. Thus, 2,4-dimethyl-5-ethoxycarbonyl-3-diazopyrrole, upon reaction with β -naphthol in aqueous sodium hydrogen carbonate solution, gave only traces of the azo dye [25LA(466)229; 30LA(483)251], whereas in refluxing chloroform, the dye was obtained in good yield. The azo dyes obtained from 2-diazopyrroles form complexes with transition metals at variance with those obtained from 3-diazopyrroles (62JCS1638).

2,5-Diphenylpyrrole 3-diazonium chloride did not couple with pyrrole and simple nonfunctional pyrrole derivatives in alkaline media. In these conditions, only the diazo compound precipitated and was isolated (61JOC3790). The same result was obtained when acetic acid was used as solvent, although pyrrole derivatives did couple with aromatic diazonium salts in the same solvent. The coupling reaction between the pyrrole diazonium salt and pyrrole derivatives took place at very mild conditions and used an inert solvent such as acetonitrile, ether, hydrocarbons, chloroform, or carbon tetrachloride (61JOC3790). Coupling of 2,5-diphenylpyrrole-3-diazonium salt with pyrroles bearing occupied α -positions led to 3,3'-azobispyrroles **184**, while coupling with pyrroles having either free α - or free α - and β -positions led to 2,3'-azobispyrroles **185**.

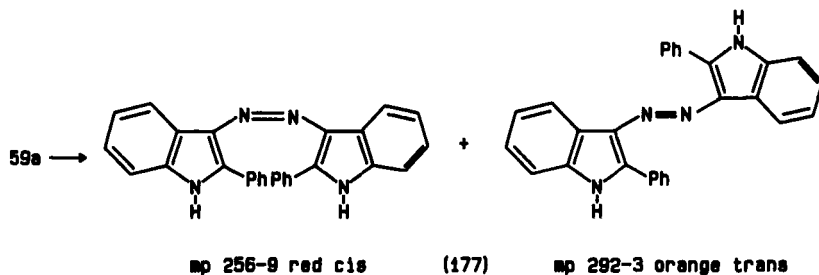
3-Diazo-2,4,5-triphenylpyrrole **44**, reacted with Grignard reagent to give the corresponding 3-alkyl-azopyrrole (10G411). Reducing agents such as zinc/acetic acid, zinc/ammonium chloride, ammonium sulfide, and hydroxylamine gave the corresponding 3-amino-triphenylpyrrole (23G795). Catalytic reduction with Pd-C in ethanol led to the 2,3-dihydro-2,4,5-triphenylpyrroline and ammonia (23G795).

2. Diazoindoles

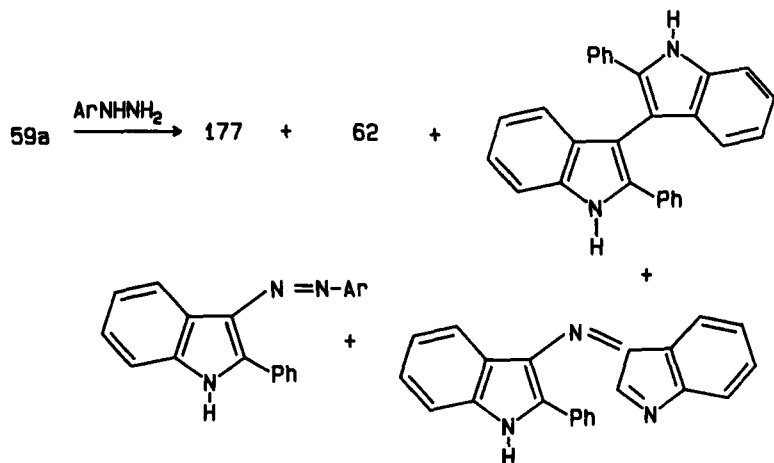
Like 3-diazopyrroles, 3-diazoindoles couple with β -naphthol in an inert solvent, although at a considerably lower rate (63JCS4593). 3-Diazo-2-phenylindole coupled in acetic acid with 2-phenylindole to give the 2,2'-diphenyl-3,3'-azoindole **177** in high yield (66LA17) (Scheme 52). Probably, the disagreement among the melting points reported by different authors for the same compound is due to the different percentage of the *cis* and *trans* isomers [66JCS(C)1345]. The same azo dye **177** was obtained, together with the hydrazo compound **176** (see Section III,B,2), by reduction of the diazo compound with ammonium chloride in ethanol/water (37G633).

3-Diazo-2-methylindole treated with an ethereal solution of iodine gave an addition product that explodes at 80°C (06G56). 3-Diazo-2-phenylindole (**59a**), up on reduction with ammonium chloride or aluminum amalgam in alkaline solution, gave ammonia and 2-phenylindole (05MI1; 06G56; 39MI1).

Compound **59a** reacted with arylhydrazines to give complex mixtures as shown in Scheme 53 (70G745). The reaction presumably goes via an electron transfer process in which the diazo compound serves as electron acceptor. Similar reactions leading to even more complex mixtures were also observed with hydroxylamine, hydrazo compounds, and conjugate indole derivatives (70G757).

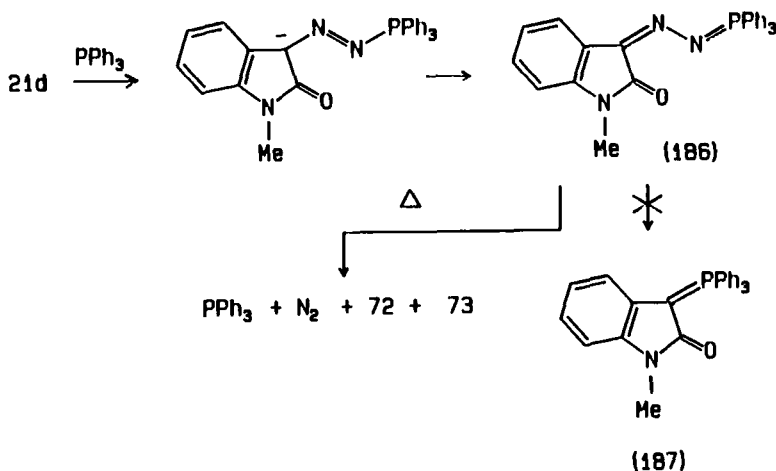


SCHEME 52



SCHEME 53

The unconventional 1-methyl-3-diazoindole (**21d**) reacted with triphenylphosphine in absolute ether at room temperature to give the phosphazine adduct **186** in high yield by a nucleophilic addition of the phosphorous to the terminal nitrogen of the diazo group (64JOC3577) (Scheme 54). It is worthy to note that the thermal decomposition of **186** yielded 1,1'-dimethylisoidindigo (**72**), 1,1'-dimethylisatinazine (**73**), nitrogen, and triphenylphosphine. Ylide **187**, though expected by analogy with the thermal



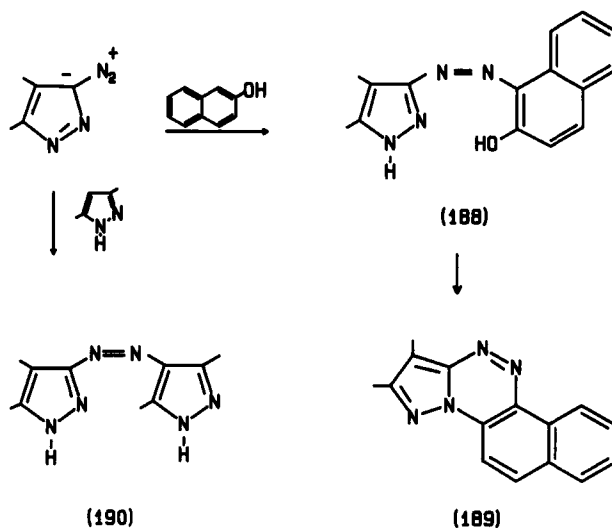
SCHEME 54

decomposition of fluorenylhydrazonotriphenylphosphorane, a carbocyclic analog of **186** that led to the ylide fluorenylidenetriphenylphosphorane, was not obtained (19HCA619).

3-Diazooxindoles, treated in methanol with mineral acids or boron trifluoride, gave the corresponding 3-methoxyoxindoles (65JOC3610). Careful regulation of the temperature is necessary to obtain good yields. When a solution of 3-diazooxindoles in ethanol or 1-propanol was similarly treated, 3-ethoxy and 3-propoxyoxindoles were formed. The formation of 3-alkoxyoxindoles could not be observed when acetic acid or other carboxylic acids were used. The mechanism involves protonation of the 3-carbon of the indole, elimination of nitrogen in the rate-determining step, and final rapid reaction of the cation with the nucleophile (63HCA983).

3. Diazopyrazoles

a. *3-Diazopyrazoles.* 3-Diazopyrazoles coupled with β -naphthol in basic aqueous solution to give the corresponding azoderivatives **188** [59G1017; 74JHC867; 79ZN(B)275] (Scheme 55). In the presence of excess alkali or in organic solvent, the cyclic compound **189** derived from dehydration of the azo dye was obtained (61CB1036). The coupling reaction also took place with several phenols, *N,N*-dimethylaniline, and dihydrox-



SCHEME 55

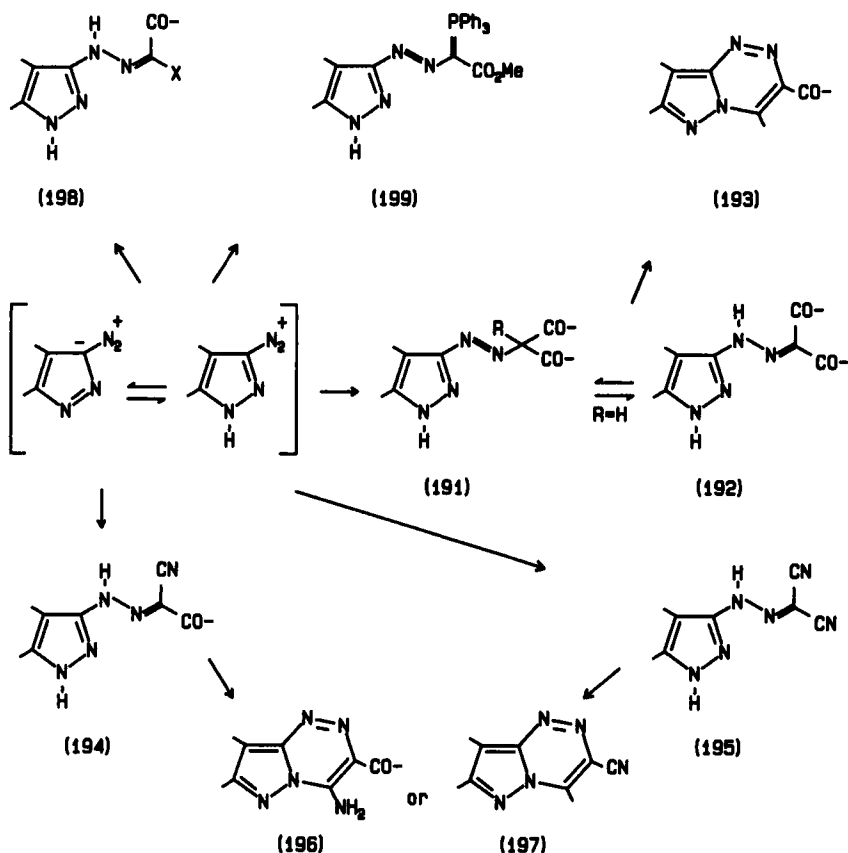
ynaphthalenes (66CB3350). Depending on the ratio of reagents employed and on the pH of the medium, different azo dyes and/or cyclic analogs of **188** and **189** were obtained.

3-Diazopyrazoles coupled with 1,6-methano[10]annulenes under mild, neutral conditions to give the corresponding azoderivatives in good yields [85AG(E)346]. Azobispyrazoles of type **190** or aminoazo compounds were formed when pyrazole derivatives were used as coupling agents or when a self-coupling reaction took place during diazotization (78KGS382; 82MI1).

3-Diazopyrazoles reacted in buffered solutions with methylene active compounds to give the corresponding coupling products that can exist either in the azo or hydrazo form when a tautomerizable hydrogen is present. Depending on the nature of the reactants and on the pH of the medium, azopyrazoles can either be isolated in good yields or can directly cyclize to pyrazolo-triazine derivatives. The reactive species undergoing the coupling reaction can be either the diazo or the diazonium form. In the latter case, the acid generated during the coupling reaction can catalyze the cyclization process. Thus, 3-diazopyrazoles coupled with β -dicarbonyl compounds to give the hydrazo derivatives **192** (Scheme 56) under neutral or basic conditions [66JCS(C)1127; 76JMC517]. With cyclic diketones such as 2-carbethoxycyclopentanone, the open-chain compound derived by a Japp-Klingemann reaction was obtained (76T725). When the azo derivatives of type **191** were unstable or very reactive, either the ring closed pyrazolo-triazines **193** or a mixture of **191** and **193** were obtained [76JOC3781; 76T725; 78ZN(B)216; 81JCS(P1)1424].

The coupling reaction of 3-diazopyrazoles with β -ketonitriles, nitrilesters, and dinitriles generally led to the hydrazo derivatives **194** and **195** (74M535; 76JMC517; 76JOC3781). In the reaction with 1-phenylethylidene malonitrile, together with the hydrazone of type **195**, an amidrazone derived from a further coupling reaction was obtained (87JHC227). In several cases the pyrazolo-triazine derivatives of type **196** and **197** could directly be obtained [76JOC3781; 78ZN(B)216; 82MI1], and ring closure was made possible either with the nitrile or the carboxy function [81JCS(P1)1424]. The reaction of 3-diazopyrazoles with substituted acetonitriles directly led to the corresponding aminopyrazolo-triazines (84CCC275).

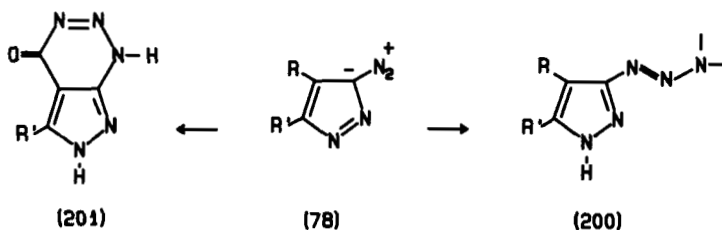
3-Diazopyrazoles coupled also with α -halocarbonyl compounds to give the corresponding halohydrazones of type **198** in good yield (77JHC227; 80JHC209). Azo coupling of 3-diazopyrazoles also took place with triphenylphosphonium- α -methoxy-carbonylalkoxide to give ylide **199**, which can further cyclize to pyrazolo-triazinone (87MI2). 3-Diazopyrazoles reacted with isopropylmagnesium chloride to give the corresponding hydrazones (84CB1726).



SCHEME 56

In organic solvents, primary amines give the monosubstituted triazeno-pyrazoles of type **200** in high yields [82AG1508; 82AG(E)698; 83JHC1629] (Scheme 57). The same reaction with secondary amines, including pyrrolidine and anilines, led to the corresponding disubstituted triazenes **200** (71JPS554; 73GEP2253615; 77JA633). In the case of 3-diazopyrazole-4-carboxamide (**78**) ($\text{R} = \text{CONH}_2$, $\text{R}' = \text{H}$), triazenes of type **200** were obtained when the reaction was carried out in organic media (69JMC545; 71JPS554), whereas in dilute aqueous basic or acidic solution, the competing intramolecular coupling reaction gave rise to the pyrazolo-triazinone **201** ($\text{R}' = \text{H}$) (68JPS1044).

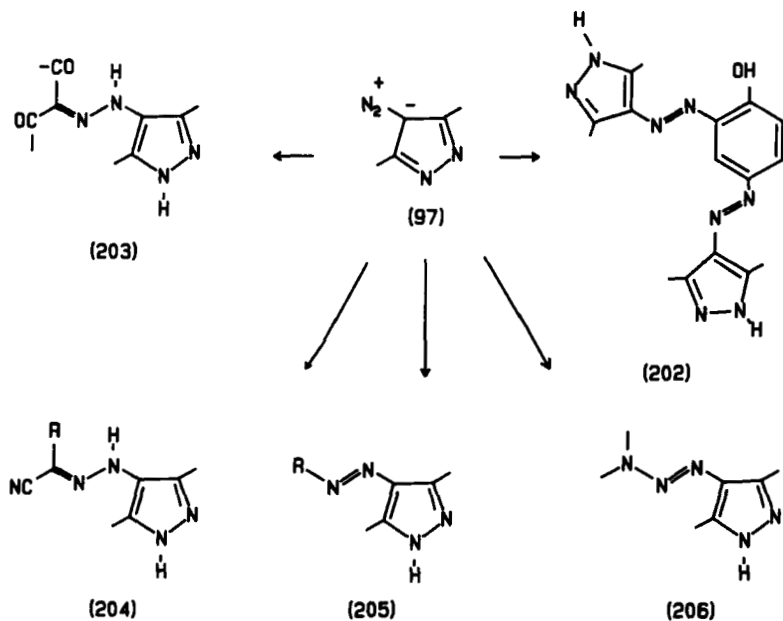
Nucleophilic substitution leading to nitro derivatives was observed when the 3-diazopyrazoles obtained by diazotization in excess nitrite were warmed in the diazotization medium with or without copper (70KGS259;



SCHEME 57

72GEP2212080). Sandmeyer reaction on the 3-diazopyrazoles gave the corresponding 3-haloderivatives in low yield (61CB1036; 66CB3350). Reduction of the 3-diazopyrazoles with stannous chloride in hydrochloric acid led to the corresponding hydrazino compound [66JCS(C)1127; 84CB1726], whereas with hydrazine, the reduction resulted in good yields of the corresponding azido derivatives (73JHC839).

b. *4-Diazopyrazoles*. 4-Diazopyrazoles coupled in boiling organic solvents with β -naphthol to give the corresponding azo dyes [61CI(L)1163; 63JCS4589]. Coupling with phenols always led to bis azo derivatives of type **202** (74YZ23) (Scheme 58). For these reactions, the initial formation



SCHEME 58

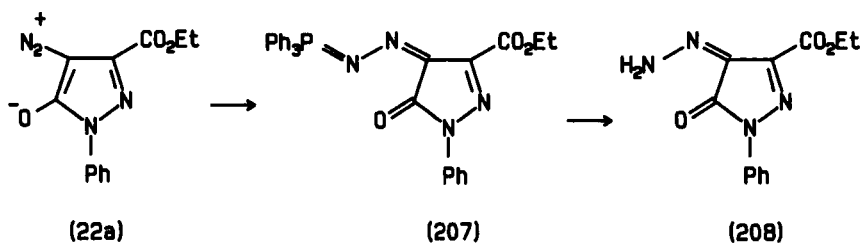
of the diazonium cation and of the phenol anion was invoked, as already seen in the pyrrole series.

The unconventional 4-diazopyrazoles behaved in analogous fashion (47USP2420791; 84JHC957; 87MI1). Coupling reaction of 4-diazopyrazoles with methylene active compounds such as β -diketones and β -carbonylnitriles always afforded the hydrazo derivatives of type **203** and **204** respectively; in this case, the dehydration process leading to the cyclic products is not allowed (74CB1555; 74YZ23; 84JHC957). Cyclic methylene-active derivatives such as dimedone and indandione were also used in the coupling reactions, and hydrazo derivatives of type **203** were obtained [78H(10)199].

In the reaction of 4-diazopyrazoles with Grignard halides, 4-alkylazo or 4-aryldiazopyrazoles of type **205** were obtained, sometimes with traces of the corresponding dediazoniated pyrazoles (74YZ23). This reaction was successfully employed in the preparation of derivatives (R = alkyl) that could not be obtained by the coupling reaction.

4-Diazopyrazoles reacted with amines and aminoacids to give the corresponding triazenes of type **206** (66YZ766; 71JMC1245). The unconventional 4-diazopyrazole **22a** reacted with triphenylphosphine to give the red colored phosphazine **207** that was easily converted into the corresponding hydrazone **208** [78H(10)199] (Scheme 59). These unconventional 4-diazopyrazoles **22** are generally very resistant to the action of alkali [60CI(L)659; 62JA1399], and only hydrolysis of the other functions (ester or amido) was observed [78H(10)199; 84H(22)2309; 87MI1]. On the contrary, 3-benzoyl-4-diazo-5-phenylpyrazole was reduced by cold methanolic potassium hydroxide to the 4-unsubstituted pyrazole [60CI(L)659].

Reduction to the corresponding dediazoniated pyrazoles was achieved by using titanium trichloride or iron(II)ammonium sulfate (79S194). The yields are moderate with ammonium sulfate and higher with titanium trichloride. The exothermic reaction that takes place with development of nitrogen is somehow slower with the iron salt, but can be completed by

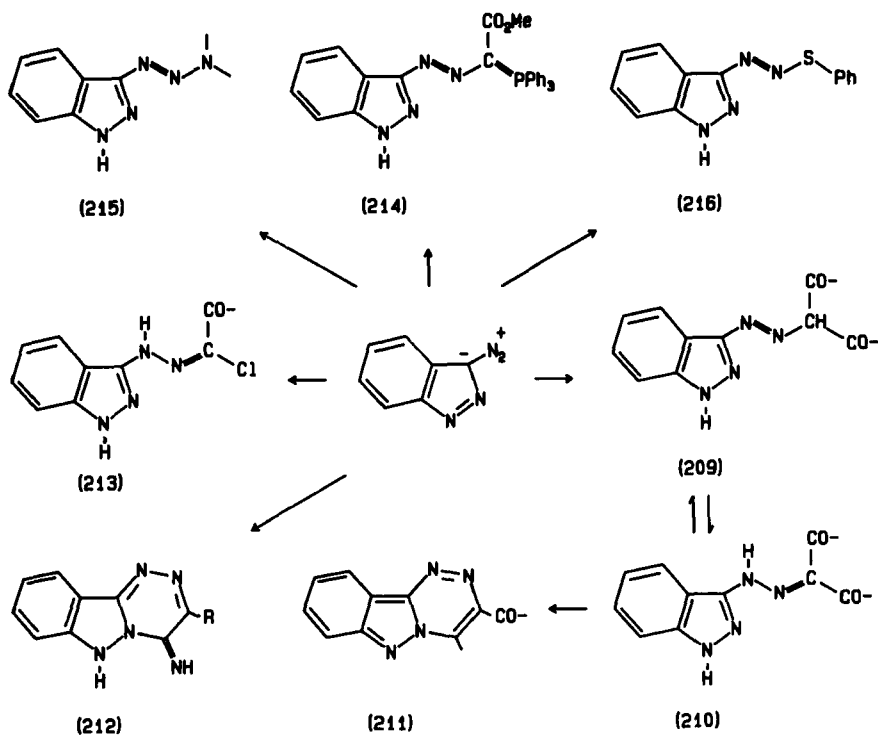


SCHEME 59

refluxing for a short time. Reduction of the diazo function to 4-aminoderivative was achieved by using sodium hydrosulfite in boiling aqueous ethanol (62JA1399).

4. Diazoindazoles

3-Diazoindazole reacted with naphthols, dimethylaniline, and 1,6-methano[10]annulenes to give the corresponding azocompounds [1899CB1773; 85AG(E)346]. Reaction in ethanol with 1,3-dicarbonyl compounds led to good yields of the azoderivatives **209**, which could also exist in the tautomeric hydrazo structure **210** (63JCS5901; 74JOC1833; 84CB1726) (Scheme 60). With cyclic diketones and methylacetoacetic acid, the hydrazones resulted from a Japp-Klingemann reaction on the primary coupling products. In some cases, triazino-indazoles **211**, derived by loss of water from the intermediate azo compounds, were directly obtained (63JCS5901; 74CB1555).



SCHEME 60

Coupling of 3-diazoindazole with substituted carbonylnitriles and dinitriles directly led to the cyclic iminotriazino-indazoles **212** (82MI2; 84CCC275). In the reaction with α -chloro-dicarbonyl compounds, 3-diazoindazole gave the hydrazonyl chlorides **213** by diazocoupling followed by a Japp-Klingemann reaction (82MI2). Azolylazoylide **214** was obtained from the coupling reaction of **2** and triphenylphosphonio- α -methoxycarbonyl-alkanide (87MI2).

Reaction of 3-diazoindazole with isopropyl magnesium chloride afforded the corresponding hydrazones (84CB1726). 3-Diazoindazole reacted with primary and secondary amines to give stable triazenes **215** (76T725). With aqueous ammonia, 3-aminoindazole and bis-indazol-3-yl-amine were obtained instead of the expected triazenes. In the reaction with thiophenol, the corresponding thioazosulfide **216** was obtained (76T725).

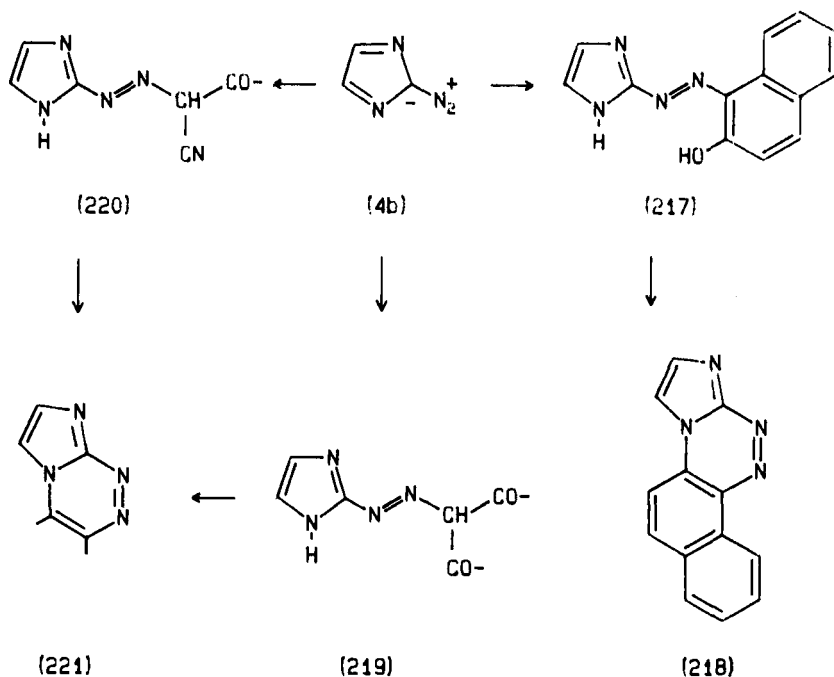
3-Haloindazoles were obtained when 3-diazoindazole was treated with hydrogen halides (1899CB1773). 3-Diazoindazole and the corresponding diazonium salts were reduced to 3-hydrazinoindazole by stannous chloride in hydrochloric acid (63JCS5901; 84CB1726). When, at the end of the reaction, alkali was added to give pH 12, several byproducts (indazole, 3-aminoindazole, and 3-azidoindazole) were also obtained (76T725). Reduction to indazole was observed when the 3-diazoindazole was reacted with titanium trichloride or iron (II) ammonium sulfate (79S194).

5. Diazoimidazoles

a. *2-Diazoimidazoles.* 2-Diazoimidazole decomposed before coupling with substituted phenols in basic or neutral media (82JHC61); however, a coupling reaction with β -naphthol led to the corresponding azoderivative **217** which easily cyclized to imidazo-naphtho-triazine **218** (74JHC867) (Scheme 61).

2-Diazoimidazole reacted with methylene active reagents such as β -diketones, β -ketoacids, and β -nitrilesters to give the azoderivatives **219** and **220** which can cyclize, upon heating, to the corresponding imidazo-triazines **221** (76JMC517). 2-Diazo-4,5-dicyanoimidazole coupled with *cis*-1,2-dimethoxyethylene to give the corresponding azo compound (73JA2695). Diazo coupling reaction of 2-diazoimidazole with pyrrolidine led to the corresponding triazene [80DIS(B) (40) 3747].

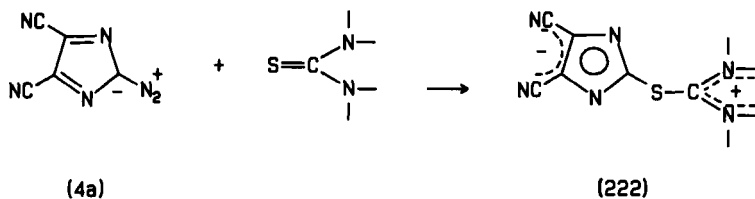
2-Azidoimidazole was obtained either by treatment of the freshly prepared 2-diazoimidazole with sodium azide (77JHC33) or by a self-coupling reaction of 2-diazoimidazole, during the diazotization reaction, followed by decomposition of the intermediate tetrazene (74MI1). Nucleophilic substitution leading to the nitro derivative was observed when the 2-



SCHEME 61

diazoimidazole was prepared in excess sodium nitrite and cupric sulfate at room temperature (65AAC469; 65JA389).

2-Diazo-4,5-dicyanoimidazole gave a stable one-to-one "host-guest" complex with 18-crown-6-ether (79JOC1717). The same diazoimidazole **4a** reacted with thiocarbamides to give the corresponding thiocarbonylides for which the betaine structure **222** with a wide charge delocalization was proposed (76TL4139) (Scheme 62). The 2-diazoimidazole **4a** was reduced with hypophosphorous acid to the dediazoniated imidazole (73USP3770764).

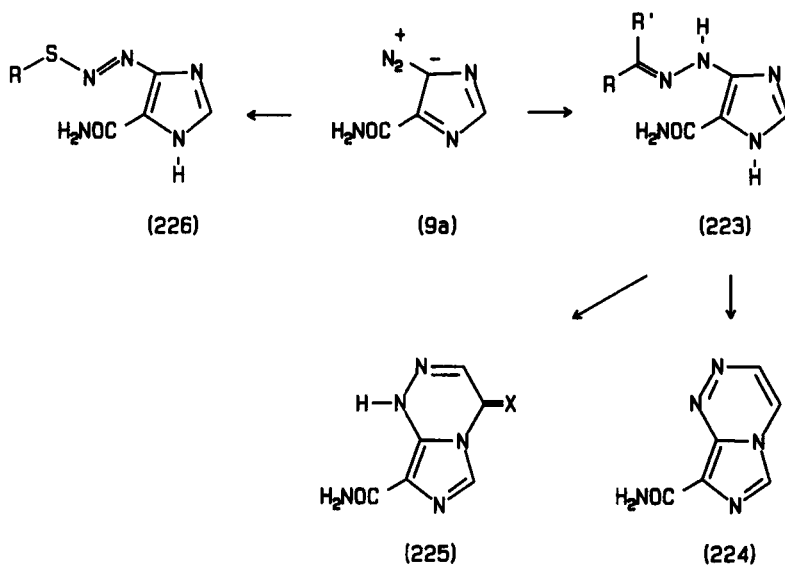


SCHEME 62

The only reactions of 2-diazobenzimidazole with nucleophiles involved the coupling with α -chloro-dicarbonyl compounds that gave the chlorohydrazones (82MI2) and the reaction with nitrite in the presence of copper sulfate which led to the 2-nitrobenzimidazole (65AAC469).

b. *4-Diazoimidazoles*. 4-Diazoimidazoles coupled in aqueous solution [83DIS(B)(44)1113] or in acetic acid [66CI(L)2197] with β -naphthol to give the corresponding azo dyes. They also reacted with *N,N*-dimethylaniline and naphthylamine to give the *C*-diazocoupled products (76KGS556; 82KFZ303). In the case of the unsubstituted 4-diazo derivative, the coupling products could not be isolated probably because of rapid hydrolysis [83DIS(B)(44)1113]. In the case of 4-diazoimidazole-5-carboxamide, the azoderivatives could be isolated only at pH 8 because of the competing cyclization to 2-azahypoxanthine (62JOC2150). This behavior was observed with heteroaromatic coupling agents such as pyrazolines [82JCS(P1)1811], aminoimidazole, and 4-carbamoylimidazolium-5-olate [81JCS(P1)1433].

4-Diazoimidazoles coupled with β -dicarbonyl compounds to give the azo compounds that, upon heating, cyclized to imidazo-triazine (76JMC517). 4-Diazoimidazole-5-carboxamide (**9a**) (Scheme 63) reacted with β -dicarbonyl compounds, but the cyclization to 2-azahypoxanthine

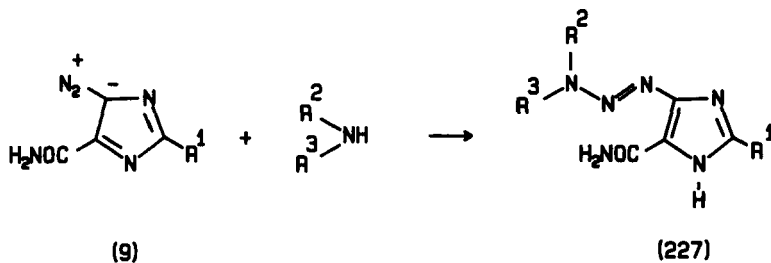


SCHEME 63

always competes; the azocoupling products could be obtained only in ethanol at room temperature (76T725). In the case of cyclic diketones, the open chain hydrazones **223** resulted from a Japp-Klingemann reaction (76T725). An improvement of the method allowed the isolation of a variety of hydrazones in generally satisfactory yields with few exceptions [81JCS(P1)1424]. Cyclization of the hydrazones **223** to imidazotriazines **224** or imidazotriazinones **225** ($X = O$) and the corresponding methylene derivatives **225** ($X = CH_2$) is generally an easy reaction, and even if there are contrasting reports, it is recognized that, in acid, the more basic derivatives were obtained, whereas in basic media, the more acidic compounds were formed [81JCS(P1)1424].

Coupling of 4-diazoimidazole **9a** with amino groups could take place either intramolecularly, as already repeatedly stated [51JBC(189)401; 61JOC2396], or intermolecularly with several primary and secondary amines. Despite the competing intramolecular cyclization in organic solvents such as methanol, ethanol, and ethyl acetate, diazoimidazoles **9** (Scheme 64) reacted with mono and dialkylamines, arylalkylamines, and cyclic amines to give pure triazenes **227** generally in good yields. Because of the biological interest of this class of compounds (Section V,B), a very large number of derivatives have been prepared; they are listed in Table XIII. Generally, the stability of the triazenes **227** is controlled by the effect of the substituent on the triazeno group, and in particular, simple alkyl groups have a labilizing effect on the monosubstituted derivatives (66JMC34; 70JPS1829). 4-Diazoimidazoles with a substituent in the 5 position different from carboxamido, such as nitro (82KFZ303), cyano [76KGS556; 82JCS(P1)1811], and alkoxycarbonyl [67JPS147; 72USP3654257], also gave the corresponding triazenes. Coupling reactions of diazoimidazoles with amidines leading to triazenes are also reported (73GEP2253615).

4-Diazoimidazole-5-carboxamide (**9a**) coupled in methanol with mercapto derivatives to give the thioazo compounds **226** [73JAP24392;



SCHEME 64

TABLE XIII
 4(5) (SUBSTITUTED TRIAZENO) IMIDAZOLES 227

R ¹	R ²	R ³	Reference
H	H	Me	66JMC34
H	H	Et	66JMC34
H	H	Propyl	68MI1
H	H	Butyl	66JMC34
H	H	<i>t</i> -Butyl	66JMC34
H	H	cycloexyl	66JMC34
H	H	CH ₂ —CO ₂ Et	66JMC34
H	H	CH(CH ₂ Ph)CO ₂ Et	66JMC34
H	H	(CH ₂) ₂ —N(Et) ₂	66JMC34
H	H	(CH ₂) ₄ —N(Et) ₂	66JMC34
H	H	(CH ₂) ₂ OH	68MI1
H	H	(CH ₂) ₂ Cl	75JPS177
H	H	Ph	84JMC196
H	H	C ₆ H ₄ —2—CO ₂ H	73JAP00828
H	H	C ₆ H ₄ —4—OMe	66JMC34
H	H	C ₆ H ₄ —4—SO ₃ H	73JAP00828
H	H	C ₆ H ₄ —4—Br	66JMC34
H	Me	Me	62JOC2150
H	Me	Propyl	68JPS1562
H	Me	Butyl	68JPS1562
H	Me	<i>i</i> -Butyl	68JPS1562
H	Me	pentyl	68JPS1562
H	Me	cycloexyl	68JPS1562
H	Me	CH ₂ CN	68JPS1562
H	Me	(CH ₂) ₂ OH	68JPS1562
H	Me	CH ₂ (CHOH) ₄ CH ₂ OH	68JPS1562
H	Me	Ph	62JOC2150
H	Et	Et	62JOC2150
H	Propyl	Propyl	76JAP(K)110564
H	Propyl	CH ₂ —Ph	68MI1
H	Butyl	Butyl	62JOC2150
H	Butyl	CH ₂ —Ph	68MI1
H	Pentyl	Pentyl	68MI1
H	Octyl	Octyl	62JOC2150
H	Benzyl	Benzyl	62JOC2150
H		—(CH ₂) ₄ —	62JOC2150
H		—(CH ₂) ₅ —	62JOC2150
H	(CH ₂) ₂ Cl	(CH ₂) ₂ Cl	66N(L)208
H	(CH ₂) ₂ F	(CH ₂) ₂ F	70JPS1358
H	(CH ₂) ₂ OH	(CH ₂) ₂ OH	68MI1
H	—(CH ₂) ₂ —O—(CH ₂) ₂ —		68MI1
Me	Me	Me	73GEP2247065
Et	Me	Me	73GEP2247065
Propyl	Me	Me	73GEP2247065
Butyl	Me	Me	73GEP2247065

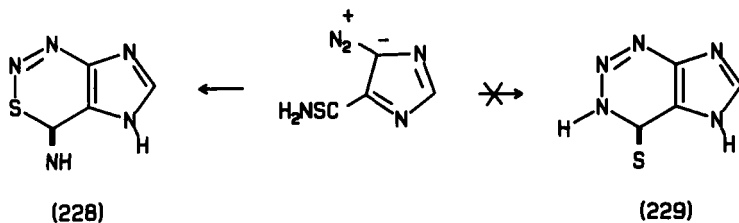
(continued)

TABLE XIII (continued)

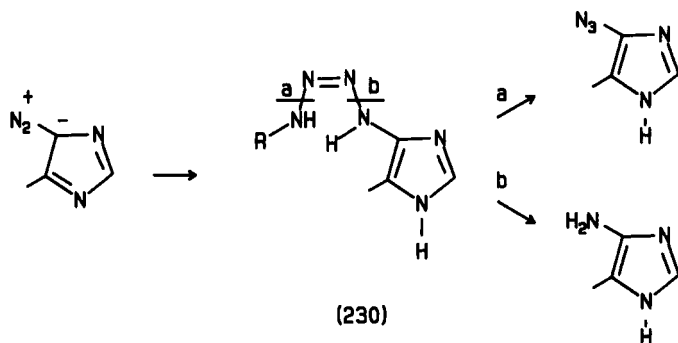
R ¹	R ²	R ³	Reference
<i>i</i> -Butyl	Me	Me	73GEP2247065
cycloexyl	Me	Me	73GEP2247065
<i>n</i> -eptyl	Me	Me	73GEP2247065
benzyl	Me	Me	73GEP2247065
(CH ₂) ₂ Ph	Me	Me	73GEP2247065
CH ₂ —CO ₂ H	Me	Me	73GEP2247065
CH ₂ —OPh	Me	Me	73GEP2247065
CH ₂ —O—C ₆ H ₄ —OMe— <i>p</i>	Me	Me	73GEP2247065
CH ₂ —C ₆ H ₄ —Cl— <i>p</i>	Me	Me	73GEP2247065
SH	Me	Me	73GEP2247065
SMe	Me	Me	73GEP2247065
SEt	Me	Me	73GEP2247065
SCH ₂ Ph	Me	Me	73GEP2247065

74JAP(K)48664. 4-Diazo-5-thiocarbamoylimidazole at pH 5 intramolecularly cyclized with the more nucleophilic sulfur to give the imidazo-thia-diazine **228** instead of the imidazotriazine-4-thione **229**, which was expected by analogy with the 4-diazoimidazole-5-carboxamide (73KGS1292) (Scheme 65).

Attempts to carry out a Sandmeyer reaction leading to 4-halo-5-ethoxycarbonylimidazole were unsuccessful, probably because of the great stability of the 4-diazo-5-ethoxycarbonylimidazole under the reaction conditions, whereas 1-substituted-4-diazonium salts showed the expected reactivity [80JCS(P1)2310]. 4-Diazoimidazoles gave high yields of the corresponding 4-azidoderivatives if reduced with hydrazines, whereas the reduction with semicarbazide and thiosemicarbazide also led to 4-aminoderivatives (73JHC839). The formation of an intermediate tetrazene **230** that could undergo scission according to pathway *a*, leading to the azido, or pathway *b*, leading to the amino derivative, was proposed (Scheme 66).



SCHEME 65



SCHEME 66

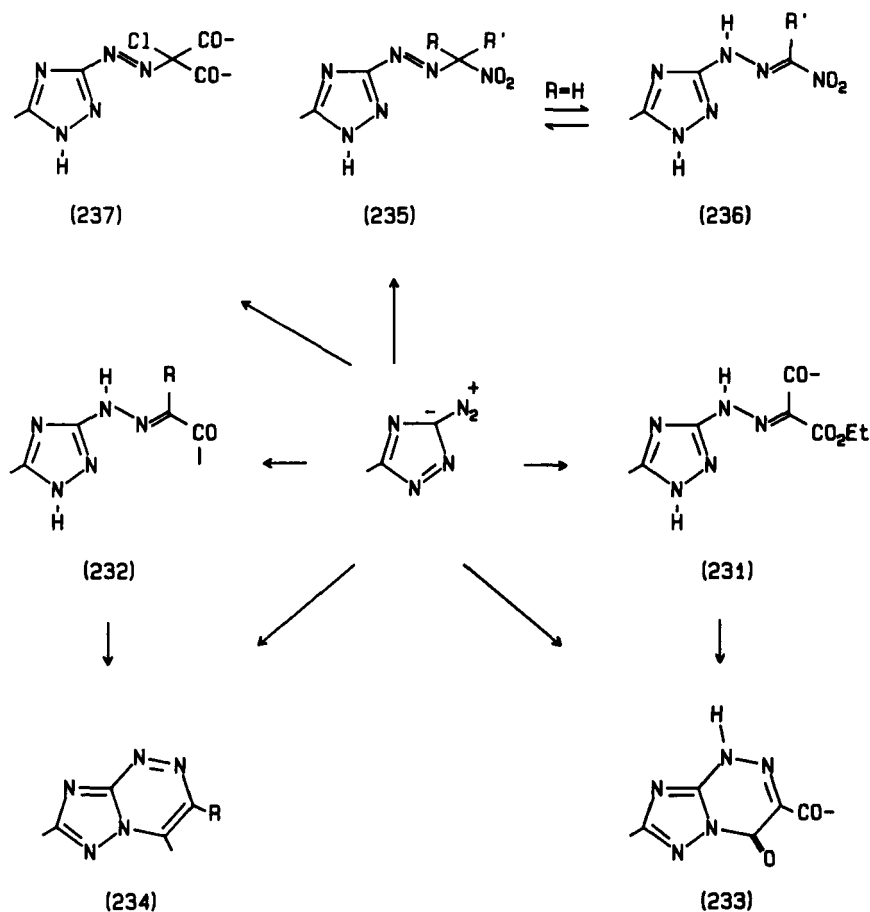
6. Diazotriazoles

a. *3-Diazo-1,2,4-triazoles*. 3-Diazo-1,2,4-triazoles coupled with naphthols in acid conditions to give the corresponding azo dyes [26JCS1729; 74JHC867; 81DIS(B)(42)1892]. The 3-diazonium salts also coupled with phenols to give azo compounds [13JPR(88)311; 34JPR(139)193].

3-Diazotriazoles reacted with several electron-rich aromatic compounds (aminonaphthalenes and anilines) to give the azo derivatives (1898LA33; 74KGS422). 3-Diazotriazoles, generated in situ by neutralization of the diazonium salts, coupled with methylene active compounds, such as β -ketoesters, β -dicarbonyls, and β -carbonylnitriles, to give either the hydrazones **231** and **232** or the cyclized products, depending on the reaction conditions [26JCS1729; 76JCS(P1)421; 76JMC517; 78ZN(B)216] (Scheme 67). The cyclic compounds **233** and **234** were directly obtained if the reactions were carried out at temperatures above room temperature or if an excess of sodium acetate was employed [76JCS(P1)1496]. With ketoesters and nitrilesters, and in the presence of sodium acetate, ring closure always took place with the ethoxycarbonyl group on the more acidic N-2.

Reaction of 3-diazotriazoles with several primary and secondary mononitroalkanes, dinitro, and trinitroalkanes led to the azo derivatives **235** [69AJC2251; 72KGS713]. In the case of primary nitroalkanes, the coupling products mainly exist in the hydrazo form **236**. The coupling reaction of α -halodicarbonyl compounds with 3-diazotriazole led to the corresponding halohydrazides **237** (80JHC209).

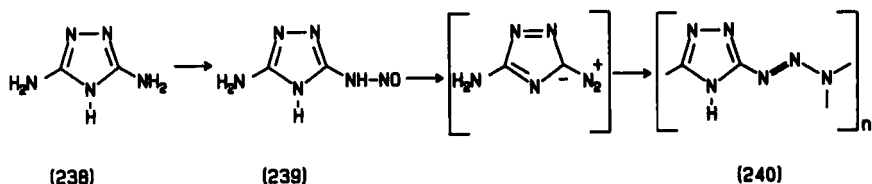
3-Diazo-5-phenyl-1,2,4-triazole reacted with methylamine to give the corresponding triazene (83JHC1629). Triazeno polymer **240** was formed by a self-coupling reaction of the diazotriazole obtained from guanazole



SCHEME 67

(**238**) (64JOC3449) (Scheme 68). Diazotization of **238** in hydrochloric acid did not lead to the polymer. In acetic acid, the intermediate nitrosoamino derivative **239** was isolated. By action of hydrochloric acid and subsequent neutralization, **239** was converted into the diazo compound that immediately self coupled.

Diazotization of aminotriazoles in excess sodium nitrite or treatment of diazo derivatives with nitrite gave the corresponding 3-nitrotriazoles by nucleophilic nitrogen replacement (69AJC2251; 70KGS259). The kinetics of this reaction were investigated in the pH range 5–7 (71ZOR1519). The reaction rate decreases with an increase in pH because of a change of the

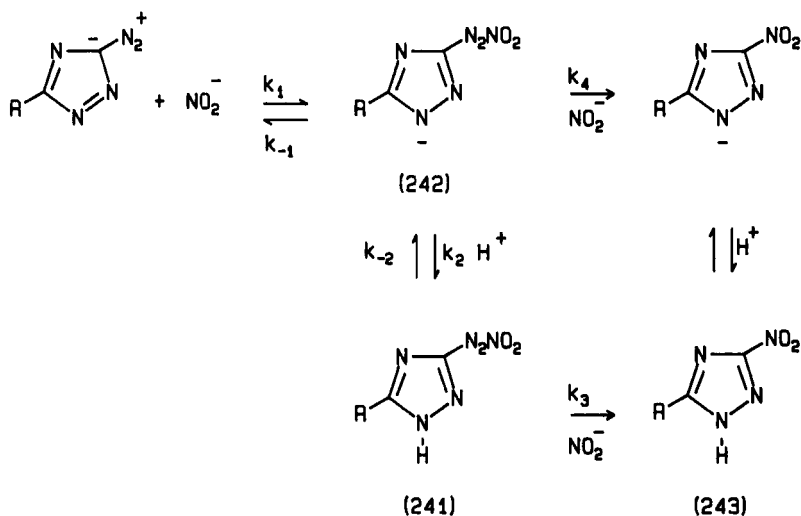


SCHEME 68

diazonium cation into an unreactive form. A weak, positive salt effect was observed in the case of the diazo acid ($R = \text{COOH}$) that reacted as zwitterion. Equation (1) was proposed for the reaction rate.

$$v = K'[\text{HetN}_2^+][\text{NO}_2^-]^{1.5} \quad (1)$$

A fractional order in the nitrite anion was found. This differs from the observed behavior in a benzene series where it is second order. The explanation, according to the Scheme 69, is based on the presence of a prototropic equilibrium between the diazonitrite form **241** and the conjugate base **242**. The nitro derivatives **243** were mainly formed from the diazonitrite **241** because the equilibrium $\text{241} \rightleftharpoons \text{242}$ is shifted towards the undissociated form, as shown by the calculated value of the quantity $k_{-1}k_{-2}/k_2k_3$.



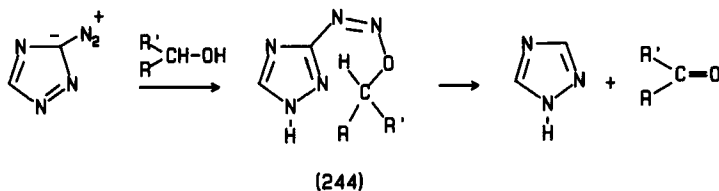
SCHEME 69

A Sandmeyer reaction leading to the 3-chloro derivatives was observed upon treatment of 3-diazotriazoles with aqueous hydrochloric acid [1898LA33; 26JCS1729; 78ZN(B)216]. 3-Diazotriazole was reduced to the parent triazole by treatment at 0°C with primary and secondary alcohols [86DIS(B) (46) 3052]. The mechanism is not clear, but the process may be envisaged as involving hydride transfer from the intermediate **244** obtained by nucleophilic addition of alcohols to the diazo compound (Scheme 70).

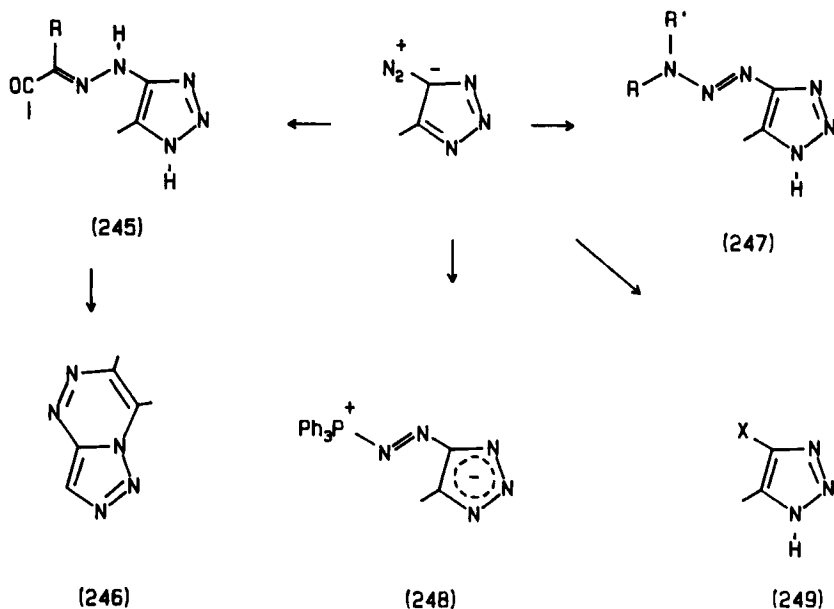
Both 3-diazotriazoles and 3-diazonium salts were converted into 3-hydrazino derivatives by reduction with stannous chloride in acids (1898LA33; 26JCS1729; 87JOC5538). 3-Diazo-1,2,4-triazole-3-carboxylic acid reacted at room temperature with sulfamic acid to give quantitatively the parent amine derivative and sulfuric acid (48JA1750). The mechanism involves the attack of the amino group of sulfamic acid on the diazo group and subsequent hydrolysis. This reaction speaks against the use of sulfamic acid to remove excess nitrous acid.

b. *4-diazo-1,2,3-triazoles*. 4-Diazotriazoles led to azo derivatives by a coupling reaction with β -naphthol (74JHC867; 75LA2159) and with *N,N*-dimethylaniline [66JMC733; 83DIS(B)(43)2557]. 4-Diazotriazoles reacted with methylene active compounds in aqueous ethanol and in the presence of sodium acetate to give only the corresponding hydrazones **245** when the carbonyl group in the resulting compounds are not reactive enough to cyclize to triazolo-triazine (75LA2159; 76JMC517) (Scheme 71). A mixture of hydrazones **245** and of triazolo-triazines **246** was generally obtained with β -ketoesters and β -ketonitriles (72TL4719), but with ethyl cyanoacetate and dinitriles, the presence of the intermediate hydrazo compounds was not observed [83DIS(B)(43)2557].

In the reaction of 4-diazotriazoles with morpholine, pyrrolidine [83DIS(B)(43)2557], and several other secondary amines (66JMC733), the corresponding triazenes **247** were obtained. Also, in the case of 4-diazo-1,2,3-triazole-5-carboxamide, these compounds could easily be obtained in organic solvents despite the competing intramolecular ring closure to 2,8-diazahypoxanthine. In aqueous media, the intermolecular coupling



SCHEME 70



SCHEME 71

reaction only occurs at suitable pH values. In fact, the intramolecular cyclization is very fast (3–8 minutes) in phosphate buffer (pH 7), whereas in hydrochloric acid, it was completed in 3 days (61JOC2396).

4-Diazo-1,2,3-triazole reacted with triphenyl phosphine in ether to give the ylide **248**, which is so unstable it rapidly hydrolyzes during filtration to triphenylphosphine oxide and triazole [83DIS(B)(43)2557].

4-Halotriazoles **249** (X = Cl, Br, I) were obtained by Sandmeyer reactions of 4-diazotriazoles [66JMC733; 83DIS(B)(43)2557]. Reduction of 4-diazo-1,2,3-triazole-5-carboxamide with semicarbazide led to a mixture of the corresponding azido- and amino-triazoles (73JHC839).

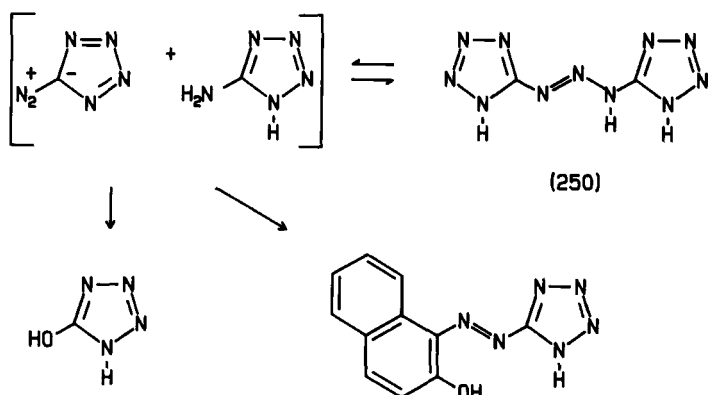
7. Diazotetrazole

Diazotetrazole coupled with α - and β -naphthols (1892LA46; 74JHC867), phenols (53AG442; 74KGS422) and other electron-rich aromatic compounds to give the corresponding azo derivatives. Diazotetrazole reacted in acid with ethyl cyanoacetate to give the hydrazone at room temperature and the ring-closed tetrazolo-triazine at higher temperatures in the presence of excess sodium acetate [76JCS(P1)1496].

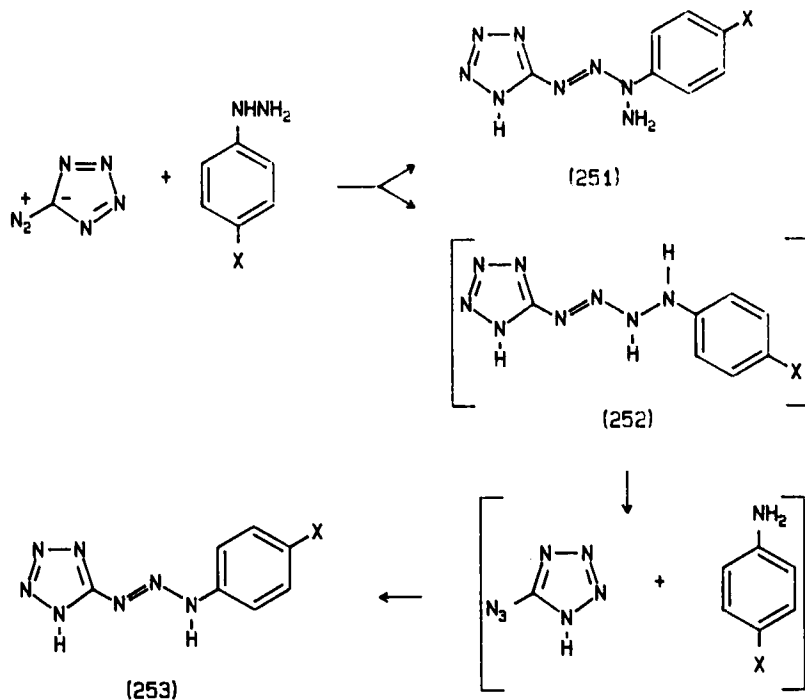
Self-coupling of the diazotetrazole during diazotization in acetic acid gave the 1,3-ditetrazolyltriazene **250** (10CB1866) (Scheme 72). Compound **250** heated in a weakly alkaline solution of β -naphthol gave an orange dye identical to that obtained by coupling diazotetrazole and β -naphthol (47N(L)644). Evidently hydrolytic cleavage of the triazene chain to diazotetrazole and aminotetrazole occurs before the coupling reaction. In fact, upon heating, the disodium salt of **250** gave the aminotetrazole and hydroxytetrazole. In this case, the diazo derivative in the absence of a coupling compound could only lose nitrogen (48M11).

Reaction of diazotetrazole with phenylhydrazine in acetic acid led to the 1,3-disubstituted tetrazene **251** ($X = H$) (58JA926) instead of the expected azide and amine (11CB2946) (Scheme 73). The reaction had the same course in hydrochloric acid, and with para substituted phenylhydrazines in addition to tetrazenes **251**, the reaction led to triazenes **253**. Formation of **253** goes through 1,4-disubstituted tetrazenes **252** followed by their rapid cleavage into azidotetrazole and the corresponding anilines and then the coupling of the aniline with the excess diazotetrazole. Formation of **251** and **252** are explicable in terms of attack of the diazo compound on N-1 or N-2 of the free base hydrazine or on the nonprotonated nitrogen of the corresponding conjugate acids.

Diazotetrazole was reduced with stannous chloride and sulfamic acid to hydrazinotetrazole [1893LA(273)144] and aminotetrazole, respectively (48JA1750). Reduction of the diazotetrazole, generated in situ, in hypophosphorous acid, gave tetrazole in high yield (54JA290). This method allows large scale preparations since the reduction of the diazo compound is fast even at 0°C; therefore, no large concentration of diazo compound



SCHEME 72



SCHEME 73

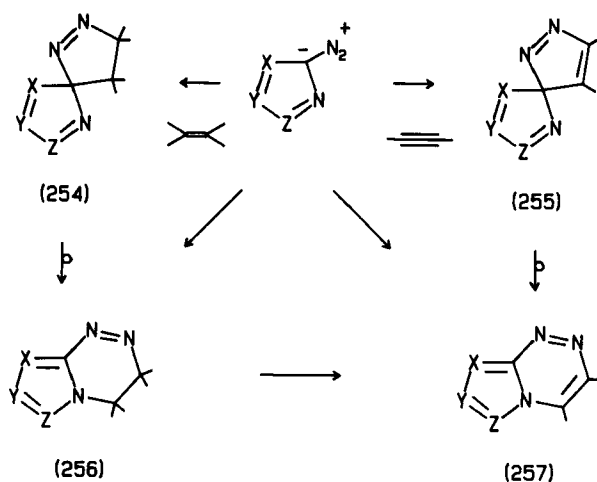
can ever exist, and consequently more concentrated solutions can be used without any danger of explosion. Moreover, this reaction is a convenient method for synthesizing tetrazole because 5-aminotetrazole is commercially available, and the direct synthesis of tetrazole is both time consuming and hazardous when used to prepare large quantities.

D. CYCLOADDITION REACTIONS

Diazoazoles, because of charge polarization and potential bifunctional reactivity of the derived betaine, react with dipolarophiles to give cycloaddition products. Generally all the diazoazoles react with electron-rich, unsaturated derivatives. The cycloaddition reaction with isocyanates is readily observed in the case of the reactive 3-diazopyrazoles, but it is much slower with other diazoazoles. By contrast, reaction with ylides and diazoalkanes is only observed for 3-diazopyrazoles and 3-diazoindazoles.

The cycloaddition reactions of diazoazoles with electron-rich and strained unsaturated dipolarophiles always led to products of type **256**, which can aromatize, or to **257** which results from a formal 1,7-cycloaddition (Scheme 74). However, for these reactions, two mechanisms are possible. The first involves a direct, thermally allowed ($4n + 2$ electron) 1,7-cyclic process that gives **256** or **257**. The second goes through the initial ($4n + 2$ electron) 1,3-cycloaddition, which leads to spirostructures **254** or **255** followed by [1,5]sigmatropic rearrangements and/or ring openings and reorganization.

Although it is still not clear which mechanism is more likely, it is known that diazocyclopentadienes give stable, isolable 1,3-cycloadducts (74S878). In the case of the diazoazoles in which there is not a nitrogen next to the reactive center, 3-diazopyrrole and 3-diazoindole, the products deriving from a formal 1,7-cycloaddition, are not formed, but the reaction products can only arise from the initial 1,3-cycloaddition and subsequent [1,5]sigmatropic shift involving the azole ring enlargement. Moreover, in the reaction of 3-diazo-4-methyl-5-phenylpyrazole and 1,1-dimethoxyethene, the intermediate spiro compound of type **254** was isolated and characterized (81TL1199; 83JOC2330). Therefore, in diazoazoles in which there is a high charge density on the diazo carbon, the 1,3-cycloaddition process is more likely, as also suggested by qualitative evaluation of highest occupied molecular orbital/lowest unoccupied molecular orbit (HOMO-LUMO) interactions (78CB2258), whereas with the electron-deficient diazoazoles, the effective 1,7-cycloaddition might occur.

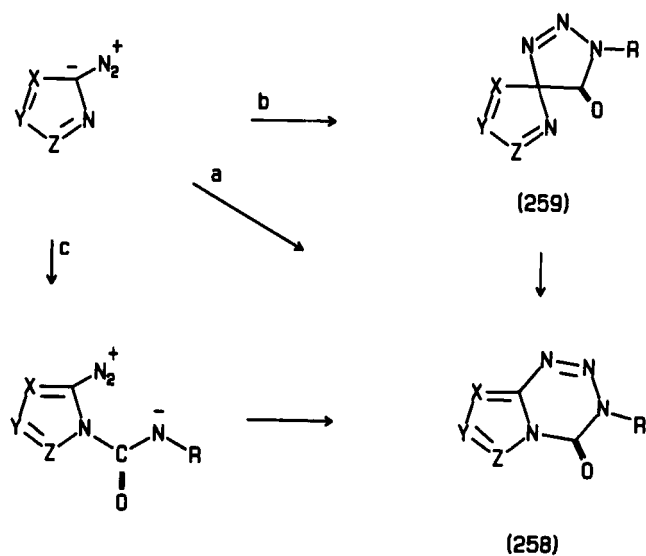


SCHEME 74

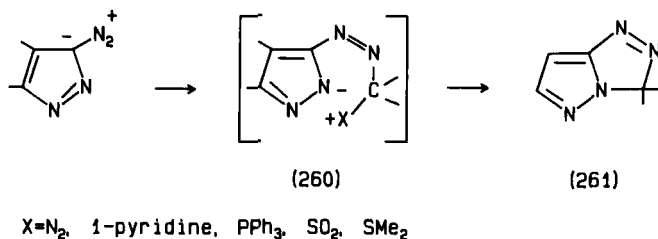
For these cycloadditions, an additional mechanism involving 1,1-cycloaddition to the nitrene-like form of the diazoazole was proposed (84CC295). These cycloaddition reactions are remarkably regio- and stereo-selective. General theoretical principles rationalize the regiochemistry of direct 1,7-cycloaddition and/or 1,3-cycloaddition in which there is electronic control in the subsequent [1,5]sigmatropic rearrangements. The diazoazoles also undergo extended cycloaddition to dipolarophiles, which are both highly electropositively and electronegatively substituted, increasing the synthetic utility of this class of compounds.

The reaction of diazoazoles and isocyanates leading to azolo-tetrazinones of type **258** (Scheme 75) can be regarded as a [7 + 2]cycloaddition of the diazoazoles to the electron-deficient hetero double-bond of the isocyanates (pathway *a*) or, alternatively, as a two-step reaction involving [3 + 2]cycloaddition of the diazoazoles to the isocyanates, leading to the spirostructure **259** and subsequent [1,5]acyl shift (pathway *b*). An additional two-step mechanism (pathway *c*) could involve nucleophilic attack by theazole ring nitrogen on the carbonyl isocyanate to give a zwitterionic intermediate that collapses to the [7 + 2]cycloadduct **258**.

Reaction of 3-diazopyrazoles and 3-diazoindazoles with ylides that behave as mononucleophile-monoelectrophiles led to the azolo-triazole of type **261** (Scheme 76). The mechanism could involve nucleophilic attack of the ylide carbon on the terminal diazo nitrogen to give **260**, followed by



SCHEME 75



SCHEME 76

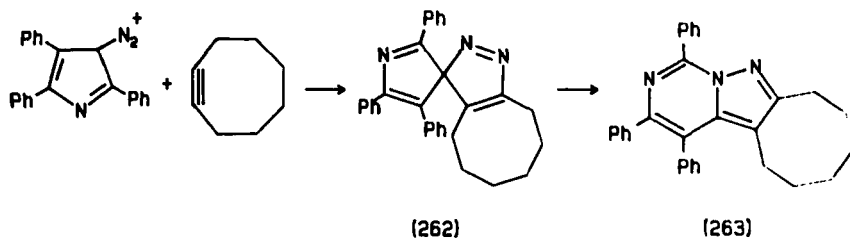
ring closure to **261** with loss of the ylide residue X or the formal $[8\pi + 4\pi]$ cycloaddition and elimination of the residue.

1. Diazopyrroles

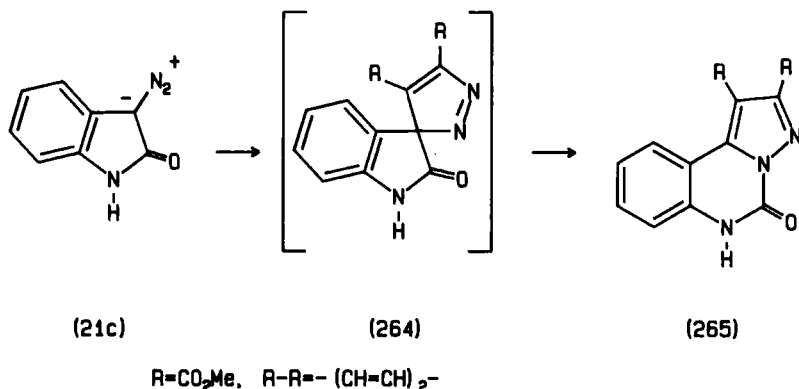
The sole example of a cycloaddition of diazopyrroles is the reaction of 3-diazo-2,4,5-triphenylpyrrole (**44**) with cyclooctyne which gave the diazaindolizine **263** (74S878) (Scheme 77). The formation of **263** goes through the initial primary adduct **262**, a $[3 + 2]$ cycloaddition product, which is destabilized by the pyrrolenine nitrogen, and undergoes a $[1,5]$ sigmatropic rearrangement which gives the pyrrole ring enlargement product.

2. Diazoindoles

3-Diazo-2-oxindole (**21c**) reacted with benzyne and dimethyl acetylenedicarboxylate in dichloromethane at 41°C to give polycyclic ring systems of type **265** (73TL1417) (Scheme 78). The intermediate spiro adducts **264** could not be detected, but it is reasonable to suppose that the final products were obtained by $[1,5]$ sigmatropic rearrangement of the carboxamido moiety.



SCHEME 77

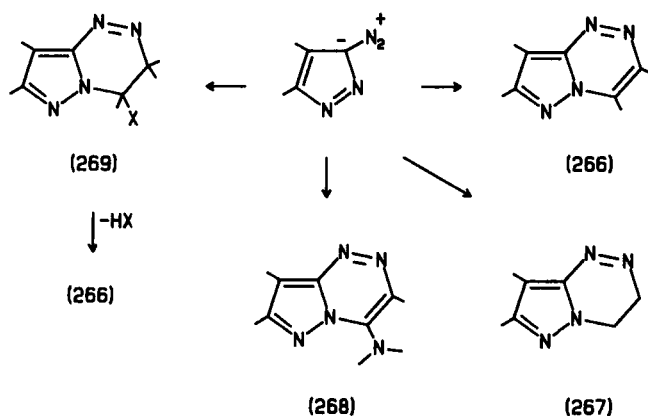


SCHEME 78

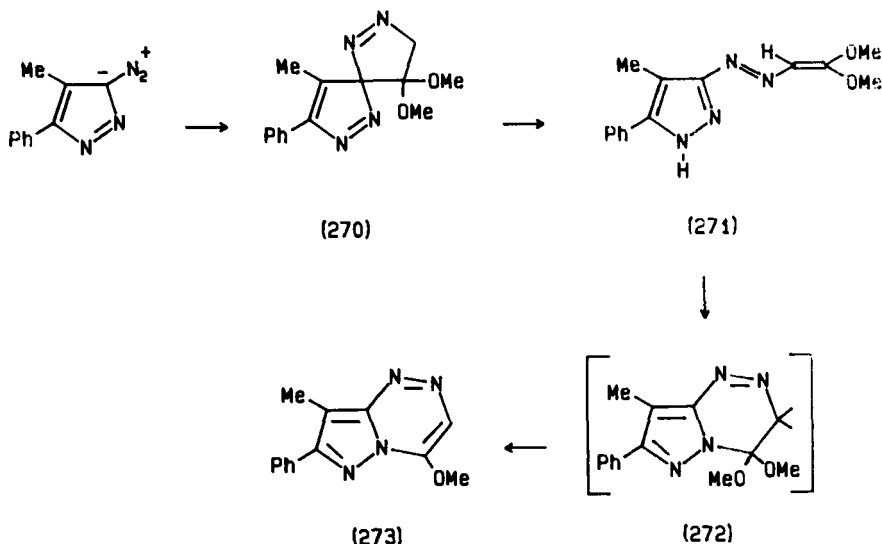
3. Diazopyrazoles and Diazoindazoles

3-Diazo-5-phenylpyrazole with acetylene dicarboxylates gives the pyrazolo-triazine **266**, and with acrylonitrile and ethyl acrylate it affords the dihydroderivatives **267** [77JHC227; 78ZN(B)216]. Similar behavior was observed in the case of the 3-diazoindazoles that led to the indazolo-triazine derivatives (type **266**) in high yields (78CB2258).

Cycloaddition reactions of 3-diazopyrazoles and 3-diazoindazoles with ynamines led to the corresponding 4-aminopyrazolo- and 4-aminoin-dazolo-triazines of type **268** (77S556; 83JOC2330). The yields are higher in the case of the 3-diazoindazoles (Scheme 79).



SCHEME 79



SCHEME 80

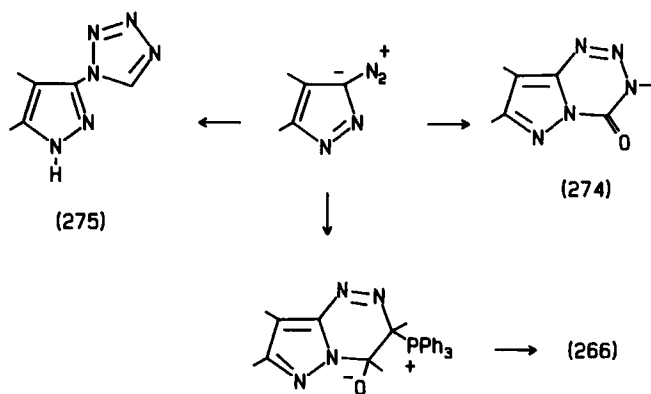
The reaction of 3-diazopyrazoles and 3-diazoindazoles in dichloromethane at low temperature with enamines and vinyl ethers gave the cycloadducts **269** which, by trans elimination of amines or alcohols, aromatize to pyrazolo- and indazolo-triazines **266** (77JA633; 78CB2258; 81TL1199; 83JOC2330; 87JOC5538). Use of 1-deuterated ethyl vinyl ether demonstrated the regiospecificity since the deuterium was exclusively located in the 4-position of the pyrazole-triazine ring (81TL1199). Evidence for the stereospecificity of these reactions was given in the case of 1-dimethyl-amino-1-ethoxy-1-butene in which different indazolo-triazines were obtained if pure *Z* or *E* isomers were used (78CB2258). In the reactions with 2,2-dialkyl substituted olefinic dipolarophiles, dihydrocompounds **269** were isolated since aromatization is impossible (83JOC2330). The reaction of 3-diazo-4-methyl-5-phenylpyrazole with 1,1-dimethoxyethene has been extensively studied (81TL1199; 83JOC2330; 86CC1127). The presence of the two discrete transient intermediates **270** and **271**, which can be isolated and characterized, was established (Scheme 80). Thus, this reaction goes through the initial 1,3-dipolar cycloaddition to give the spirocompound **270**, which isomerizes to the second transient **271**. Compound **271** slowly rearranges to the stable methoxypyrazolo-triazine **273** probably through **272**, which aromatizes by elimination of methanol.

3-Diazopyrazoles and 3-diazoindazoles reacted with monoisocyanates in ethyl acetate or dichloromethane at room temperature to give, in good

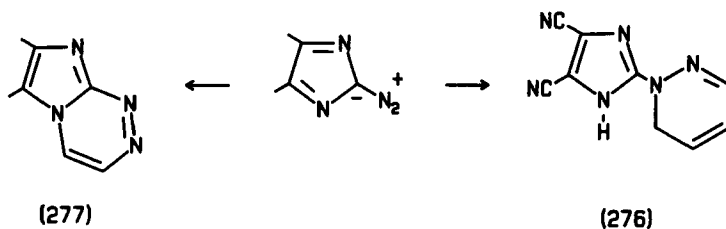
yields, the pyrazolo- and indazolo-tetrazinones **274**, and with diisocyanates, they afforded the corresponding bis-pyrazolo- and bis-indazolo-tetrazinones (79TL4253; 87JMC357) (Scheme 81). Cycloaddition to give the same type of compounds **274** was surprisingly observed in the pyrazole series with phosphonimines. In fact, these were converted into isocyanates by preliminary reaction with carbon dioxide (79TL4253).

Reactions of 3-diazopyrazoles and 3-diazoindazoles with ylides gave the 3*H*-pyrazolo- and 3*H*-indazolo-triazoles **261** after elimination of the residue HX (see Scheme 76). In the reaction with diazomethane, loss of nitrogen is verified from the diazoalkane (79TL1567). Reaction with substituted diazoalkanes is slower if electron acceptor groups are present, and with 1-diazo-1-phenylethane or diazodiphenylethane, only traces of the cyclic products were formed (84CB1726). The bicyclic compound was not formed in the reaction of pyrazole-3-diazonium chloride with diazomethane in excess; instead, 1,3-dipolar cycloaddition leading to the tetrazolyl derivative **275** took place (70CB2821).

In the reactions with phosphonio- α -methoxycarbonyl-alkanides, the products of type **261** derived from 1,3-cycloaddition can rearrange to the tautomeric 1*H*-pyrazolo-triazole (87MI2). The reaction of 3-diazopyrazoles and 3-diazoindazole with acyl-substituted phosphonium ylides led to pyrazolo-triazine and indazolo-triazine derivatives **266** instead of the expected triazole compounds (81JHC675). In this case, the ylides, which can exist as phosphonium enolates, possess nucleophilic and electrophilic centers in a β -relationship, giving [7 + 2] or [11 + 2]cycloaddition reactions. With dimethylsulfonio- α -aroyl-methanides, very complex, temperature-dependent mixtures were obtained, in some cases with sulfur retention (87MI3).



SCHEME 81



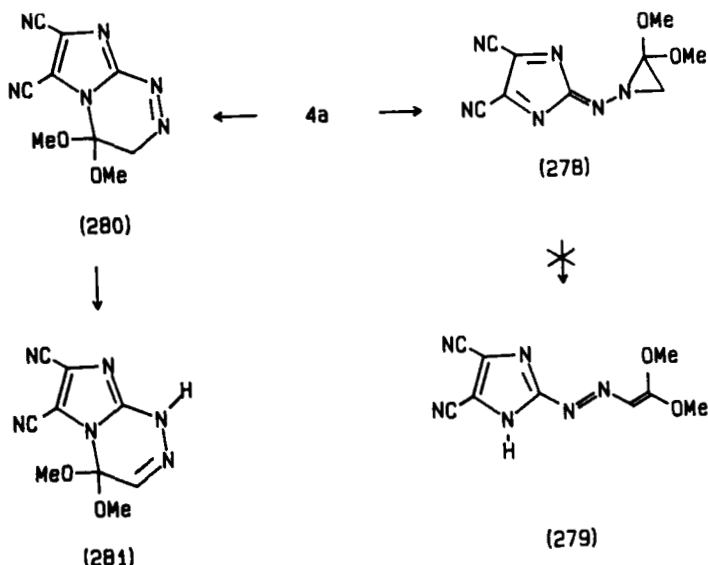
SCHEME 82

4. Diazoimidazoles

2-Diazo-4,5-dicyanoimidazole reacted with butadiene to give the pyridazinyl-imidazole **276** (73JA2695; 84CC295) (Scheme 82). 2-Diazoimidazoles, especially when cyano groups are present, undergo cycloaddition very easily with electron-rich olefins, enamines, and ketene acetals to give the imidazo-triazines **277** (87JOC5538). The stereochemistry of these cycloaddition reactions was studied in the case of strained cyclic olefins, norbornene, norbornadiene, and dicyclopentadiene, and in each case, the electrophilic addition of the diazoimidazole preferentially occurs on the face of the olefinic center having the higher electron density (87JOC5538).

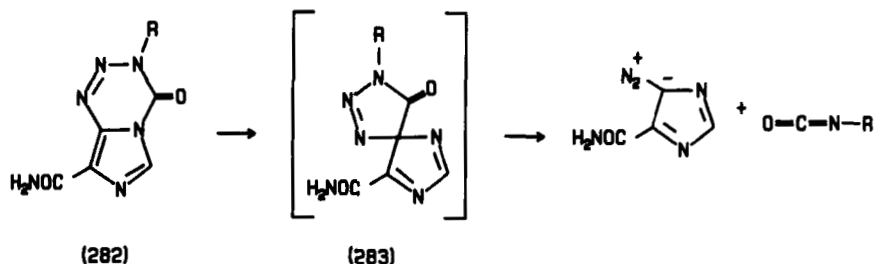
The reaction of 2-diazo-4,5-dicyanoimidazole (**4a**) with 1,1-dimethoxyethene is controversial with regard to the product and the mechanism. In fact, it was first reported that the reaction afforded the imidazolyazoethene **279** through a transient aziridine **278** that underwent ring opening followed by a hydrogen atom transfer (Scheme 83). The 1,1-cycloaddition reaction leading to **278** was proposed to proceed through attack of the terminal nitrogen atom of the diazo compound, in its nitrene-like form, on the π -system of the dimethoxyethene (84CC295). Actually, for the nitrene type 1,1-cycloaddition to proceed effectively, the diazo group has to possess a high-lying occupied π_z orbital with a suitable coefficient at N-1. For this reason, this type of reactivity has been proposed for a system such as 2-diazo-4,5-dicyanoimidazole in which the dicyanoimidazole ring is a strong electron acceptor, while the ring nitrogen lone pairs may donate electrons into the π_y system. However, structure **279** was disproved by NMR spectroscopic data, and the correct structure **281** was assigned (86CC1127). Regarding the mechanism, the formation of the diazirine intermediate was believed unlikely since, according to MNDO SCF-MO calculations, species of type **278** are predicted to lie ~ 160 kJ mol⁻¹ above the other intermediate species **280** (86CC1127; 87JOC5538).

4-Diazoimidazole also adds to electron-rich dipolarophiles, such as 1-morpholinylcyclohexene, by net 1,7-cycloaddition and subsequent elimi-



SCHEME 83

nation (87JOC5538). Both 2-diazoimidazoles and 4-diazoimidazoles give cycloaddition reactions with alkyl and aryl isocyanates, and the corresponding imidazo-tetrazinones were obtained in high yields (87JMC357; 87JOC5538). This cycloaddition reaction plays a very important role in the 4-diazoimidazole series; many imidazo-tetrazinones of type **282** are effective in anticancer therapy (84JMC196) (Scheme 84). In fact, a large number have been synthesized for pharmaceutical purposes (Section V,B). Moreover, retrocycloaddition processes that gave rise to the diazoimidazole via unstable spirobicycles **283** operate when imidazo-tetrazinones **282** are decomposed in nonnucleophilic solvents, whereas in other media, differ-



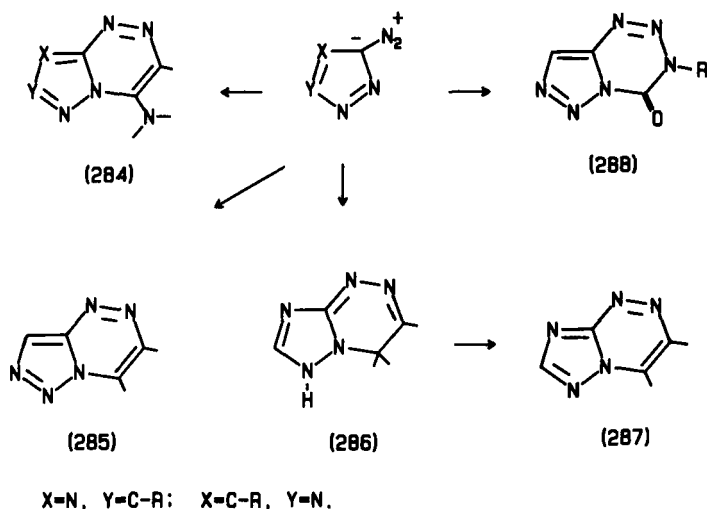
SCHEME 84

ent products such as aminoimidazole and imidazo-triazenes were obtained. This type of reactivity lends weight to the hypothesis that bicyclic tetrazinones can be a stable prodrug modification of the imidazo-triazenes [84JMC196; 87JCS(P1)665].

5. Diazotriazoles

Both 3-diazo-1,2,4-triazoles and 4-diazo-1,2,3-triazoles easily give cycloaddition reactions with ynamine leading to 4-aminotriazolo-triazine **284** and the yields are generally higher than in the pyrazole and imidazole series (77S556) (Scheme 85).

Among the diazoazoles, 3-diazotriazoles and 4-diazotriazoles are the most reactive towards electron-rich olefins, and 4-diazo derivatives can also add to less electron-donating olefins such as 1-morpholinyl-2-nitroethene (83JOC2330; 87JOC5538). In these reactions, 4-diazotriazoles, by regiospecific cycloaddition and subsequent aromatization, give a single isomeric triazolo-triazine of type **285**. With 3-diazotriazoles, the same process leading to **287** was observed with 1-substituted cyclohexenes, whereas with β -diethylaminostyrene, the 1 : 1 cycloadduct of type **286** was obtained with retention of the diethylamino residue (83JOC2330). The dihydro derivatives **286**, of course, were also obtained in the case of 2,2-disubstituted vinyl ether and enamines and with 1,1-dimethoxyethene (83JOC2330). Another feature of the reactions with 3-diazo-1,2,4-triazoles



SCHEME 85

is the possibility of competitive 1,7-cycloaddition on nitrogen in the 2- and 4-position of the triazole moiety. Considering that in 3-diazo-1,2,4-triazoles, the nitrogen is more nucleophilic in the 2- than in the 4-position, it is not surprising that this electronic effect controls the regiochemistry of polar 1,7-cycloaddition and always yields a single isomer.

The reaction of 4-diazo-5-phenyl-1,2,3-triazole with isocyanates, leading to triazolo-tetrazinones **288**, is slower than in the case of diazopyrazoles and diazoimidazoles, as could be expected from a mechanistic evaluation (79TL4253).

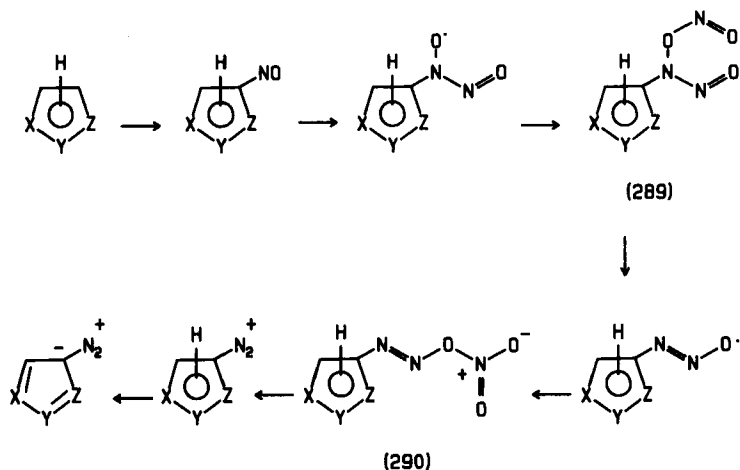
IV. Synthesis

The synthetic methods available to prepare the diazoazoles can be divided into two classes. The first involves the direct introduction of a diazo function into the azole ring; the second is the conversion of other functional groups into diazo. The direct introduction of the diazo group presents interesting mechanistic aspects but finds application, limited to a few derivatives, only in the pyrrole and pyrazole series, and it is not reliable for preparative scale syntheses. Among the reactions involving transformation of other functional groups into diazo unit, the most important is, of course, the diazotization of the corresponding aminoazole. This method was successfully employed in the synthesis of derivatives in all the series.

A. BY DIRECT INTRODUCTION OF THE DIAZO GROUP

Treatment of an azole derivative having an unsubstituted position with an excess of sodium nitrite in weakly acid media or in buffered conditions at low temperature directly led to the corresponding diazo compounds. The mechanism of the direct introduction of the diazo group involves formation of the nitroso derivative by action of nitrous acid or dinitrogen trioxide (59T288). Further addition of 2 mols of NO leads to the intermediate **289**, which, by either homolytic dissociation and readdition or intramolecular rearrangement, gives **290**. Loss of nitrate from **290** affords the diazonium species that, by base-acid interaction, gives the diazoazole (Scheme 86).

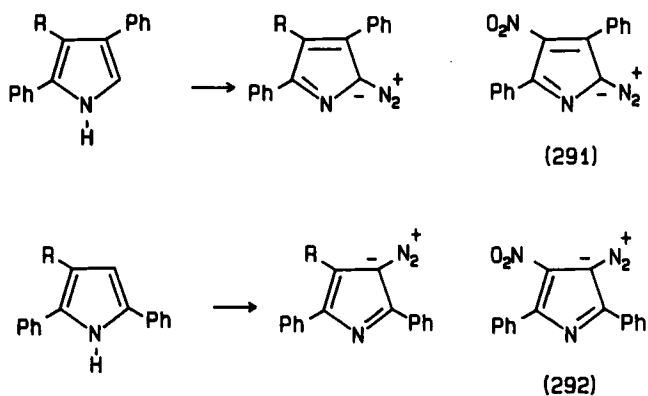
Thus, by using this reaction, either 2-diazo or 3-diazopyrroles could be prepared from the parent compounds with only one position free (60JCS3270; 62JCS1638). The reaction is slower in the case of 2-diazopyrroles and the yields are lower. In pyrroles with two unsubstituted



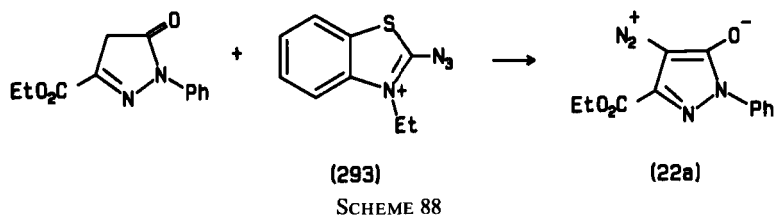
SCHEME 86

positions ($R = H$), nitration also took place after the introduction of the diazo group, and the 2-diazo-4-nitro and 3-diazo-4-nitro derivatives **291** and **292** were obtained as main products (Scheme 87).

Direct introduction of a diazo group upon treatment with an excess of nitrites was also an effective method to synthesize 4-diazopyrazoles. The dimethyl derivative was prepared in good yield in strong acid [61CI(L)1163], whereas the diphenyl derivative was only obtained in acetic acid in the presence of acetic anhydride (63JCS4589). Catalysis by mercuric acetate was also observed (63JCS4589). Direct introduction of a



SCHEME 87



diazo group using this method was unsuccessful in the case of indoles; the reaction stopped at the nitroso stage which exists almost entirely in the unreactive oxime form (63JCS4593). Similarly, indazoles and imidazoles failed (63JCS4589).

Direct introduction of the diazo group in an azole ring was also observed when the azolium salts were treated with azides. This method was successfully employed to prepare diazocyclopentadiene, and the mechanism of this reaction was also discussed (53JA5955). However, in the synthesis of diazoazoles, this method is not of general application. In fact, only traces of 3-diazopyrrole could be detected when the lithium salt of 2,5-dimethylpyrrole was treated with tosyl azide (60JCS3270). 2-Substituted indoles can be converted into the corresponding 3-diazo derivatives in good yield by diazo-group transfer using tosyl azide in a water/benzene two-phase system with sodium hydroxide as the base and triethylammonium chloride as the catalyst (81S741). In another attempt carried out in a homogeneous phase and in the absence of ammonium salt, the 3-diazoindoles could not be detected, but only 3,3'-azobisindoles were formed.

3-Carbethoxy-4-diazo-1-phenylpyrazol-5-one (**22a**) (Scheme 88) was synthesized in 76% yield under mild conditions by direct introduction of the diazo group with the azidinium salt **293** in sulfuric acid at room temperature [78H(10)199]. The easy introduction of the diazo group probably occurred because the α position of the ester was activated. On the contrary, tosyl azide failed to give the diazo derivative under the same conditions. Diazo transfer with this reagent only takes place under alkaline conditions, but in these reaction conditions, the diazo compound couples with the starting material.

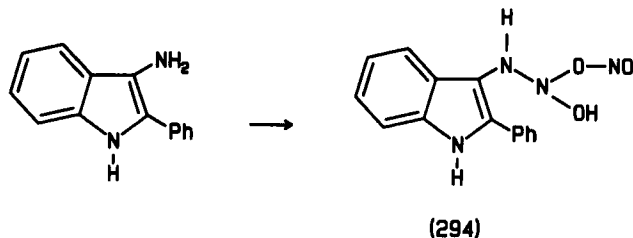
B. BY CONVERSION OF FUNCTIONAL GROUPS

The most traditional method used to obtain diazo compounds involves the diazotization reaction of an amino group, followed by neutralization of

the resultant diazonium salt. This method has, of course, found wide application in the synthesis of diazoazoles. The major problem in azole series concerns the availability and/or stability of the starting amino derivatives.

In the thirties, the only example in diazoazole series of an addition product of dinitrogen trioxide to an amino group was isolated (38G733). In fact, interruption of the diazotization of 3-amino-2-phenylindole by dilution with water and neutralization with ammonia allowed the isolation of the addition product that, in our opinion, could be represented by structure **294** (Scheme 89). This compound, dissolved in glacial acetic acid, quantitatively gave the diazo compound. A solution of **294** in water, as well as in diluted acetic acid, hydrochloric acid, and concentrated hydrochloric acid did not give the typical reaction of the nitrous acid. In glacial acetic acid, it was possible, instead, to observe the formation of a dye by the coupling reaction of novocaine hydrochloride and β -naphthol brought about by the generation of nitrous acid from compound **294**. The formation of **294** is in agreement with studies demonstrating that, in the diazotization reaction carried out at low acidities, the actual attacking species is the nitrous anhydride, a carrier of NO^+ (78MI1).

Another functional group that can be converted into diazo is the nitroso group. This transformation is a variation in the direct introduction of a diazo group. In fact, the yields are generally higher when the intermediate nitroso derivative can be isolated, purified, and further oxidized with nitrous acid or dinitrogen trioxide (60JCS3270). Examples of oxidation of hydrazones, tosyl hydrazones, and oximes to the diazo group are also reported for the preparation of the diazoazoles, and usually better results are obtained using tosyl hydrazones as starting material (64JOC3577). Diazoazoles can also be synthesized from fully substituted azoles if they contain readily displaceable groups such as acid or ester (62JCS1638).



SCHEME 89

1. Diazopyrroles

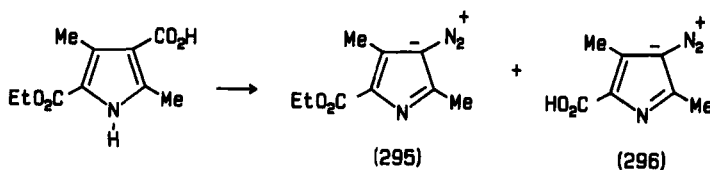
Only 3-diazopyrroles have been prepared by diazotization of the corresponding amino compounds. The reaction is carried out in acetic acid with a stoichiometric amount of nitrite in the case of simple aryl pyrroles. The diazopyrroles were isolated in good yields upon alkalization with sodium carbonate, and care was taken to control temperature during diazotization and neutralization (61JOC3790).

With less electron-rich pyrroles, hydrochloric acid can be used in the diazotization. The diazo compounds were isolated after neutralization with aqueous ammonia [84H(22)2269]. 3-Diazo-2,5-diphenylpyrrole, although efficiently prepared by diazotization of the 3-aminopyrrole, can also be prepared by oxidation of the 3-nitrosopyrrole with dinitrogen trioxide (60JCS3270). Pyrrole-3-carboxylic acid, with buffered nitrous acid, gave the 3-diazo derivative **295** by displacement of the carboxyl group, together with the 3-diazo-2-carboxylic acid **296**, obtained by further hydrolysis (62JCS1638) (Scheme 90).

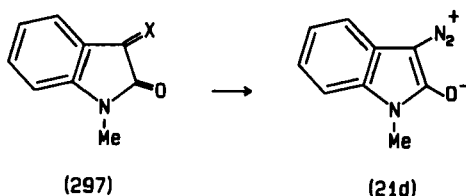
2. Diazoindoles

3-Diazoindoles were prepared in good yields by diazotization of the corresponding 3-aminoindoles in acetic acid with a stoichiometric amount of nitrite and subsequent neutralization with sodium carbonate (06G56) or aqueous ammonia (66LA17). Careful regulation of the temperature is necessary during the preparation of 3-diazo-2-phenylindole because if the diazotization reaction is carried out at room temperature or higher, only the azo compound **177** is obtained (37G633).

The unconventional 3-diazoindoles were prepared by oxidative conversion of hydrazones and oximes. Thus, 1-methyl-3-diazo-2-oxindole (**21d**) was prepared by mercuric oxide oxidation of 1-methylisatin-3-hydrazone **297** (X = NNH₂) in benzene at room temperature (1891JPR551) (Scheme 91). It can also be prepared by decomposition of 1-methylisatin-3-tosylhydrazone **297** (X = NNHTs) with aqueous sodium hydroxide in a two-



SCHEME 90



SCHEME 91

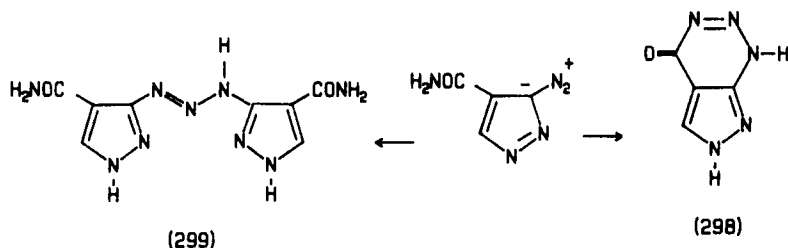
phase system (water/dichloromethane) at room temperature first, and then with gentle heating, or by chloramine oxidation of 1-methylisatin-3-oxime **297** (X = NOH) in alkaline aqueous medium at low temperature (64JOC3577). All these methods allow mild conditions and easy isolation of the product, but the second one led to the diazo compound in higher yields.

Attempts to prepare 2-diazo-3-oxindole failed. In fact, base decomposition of the isatin-2-tosylhydrazone under conventional conditions with potassium hydroxide at room temperature led to the potassium salt (64JOC3577). When an aqueous solution of the potassium salt was heated at 70°C, indigo blue was obtained in 62% yield.

3. Diazopyrazoles and Diazoindazoles

Generally, diazopyrazoles and diazoindazoles are synthesized from the corresponding amino derivatives. The diazotization reaction does not present any particular difficulty, so diazopyrazoles and diazoindazoles can easily be isolated in good yields. Aqueous solutions of alkaline nitrites are generally employed as diazotizing agents, but the use of isoamyl nitrite in organic solvents is also reported (74CB1555; 87JMC357). Different types and mixtures of acids were used, ranging from weak acetic acid to strong tetrafluoroboric acid.

Regulation of the acidity of the medium is necessary only when there is competition with an intramolecular ring closure. Thus, 3-diazopyrazole-4-carboxamide can only be isolated if the diazotization reaction is carried out in dilute hydrochloric acid or when aminopyrazole hemisulfate is used instead of the free base (68JPS1044; 71JPS554). In the presence of excess hydrochloric acid or in a large scale preparation, compounds **298** and the bis pyrazolyl-triazene **299** were also obtained (71JPS554) (Scheme 92). The same behavior was observed during the synthesis of 4-diazopyrazole-3-carboxamide (70JHC863; 71JMC1245). Neutralization of the reaction mixture can be accomplished by a wide variety of bases.



SCHEME 92

4. Diazoimidazoles

Synthesis of diazoimidazoles is generally carried out by diazotizing the corresponding amino compounds. Some precautions must be taken during the diazotization reaction, especially if the starting aminoimidazole is unstable. In fact, to obtain 4-diazoimidazole, it is necessary to generate *in situ* the 4-aminoimidazole from the corresponding imidazolecarbamate [83DIS(B)1113]. This reaction, actually, might be regarded as a conversion of the carbamoyl group into a diazo function.

Often it is necessary to carry out the reaction at low temperature, between -20° and -10°C , because of the instability of the diazoimidazoles (74MI1; 87JMC2222).

Nitrite salt in strong acids is generally used in these syntheses. The use of excess nitrite is effective in limiting the competing cyclization reaction, during the preparation of 4-diazoimidazole-5-carboxamide (62JOC2150), that can be isolated in high yield only under strict control of the reaction conditions (61JOC2396). Some diazoimidazoles may either precipitate during the diazotization reaction (73JA2695; 73USP3770764) or be extracted with organic solvents from the acidic medium (67JPS147; 72USP3654257). In the imidazole series oxidation of a nitroso group has been employed to synthesize 4-diazo-5-phenylimidazole (87JMC357).

5. Diazotriazoles

3-Diazo-1,2,4-triazoles and 4-diazo-1,2,3-triazoles are easily synthesized from the corresponding aminotriazoles. In addition to one report on a diazotization carried out in acetic acid by using isoamyl nitrite (61JOC2396), the diazotization reaction is usually achieved with nitrite salts in strong acids such as hydrochloric, nitric, sulfuric, and tetrafluoroboric acids [77S556; 81DIS(B)(42)1892]. Because of the high acidity of

the triazole system, the diazo compounds can be isolated from acid without neutralization.

An example of a diazotization reaction of a tosylaminotriazole in sulfuric acid has been reported to give the corresponding diazo compound, following hydrolysis of the tosyl group (75LA2159).

6. *Diazotetrazole*

Diazotetrazole was the first diazoazole synthesized by diazotization of diluted solutions of the aminotetrazole in hydrochloric acid with sodium nitrite; subsequent neutralization with alkali was not necessary (1892LA46). Diazotization with isoamyl nitrite in THF and aqueous hydrochloric acid was also effective and allowed the isolation of the diazotetrazole (72JA1379). When the aminotetrazole was diazotized with sodium nitrite in acetic acid, only the 1,3-ditetrazolyltriazene **250** was obtained (10CB1866).

V. Applications

Diazoazoles have found wide application. Among the biological applications is the remarkable antineoplastic activity of several diazoazoles and in particular of 4-diazoimidazole-5-carboxamide. Chemical applications are extensive because of the high reactivity and versatility of the diazo/diazonium function.

A. BIOLOGICAL AND MEDICAL USES

1. *Diazoindoles*

The diazo group confers a broad spectrum of activity on the 2-substituted indoles. In fact, 3-diazo-2-substituted indoles are effective against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Salmonella typhi* and *Proteus vulgaris* bacteria (65MI1), and 3-diazo-2-ethoxycarbonylindole inhibits sarcoma 180 in mice and rats (83KFZ1183).

2. *Diazopyrazoles*

3-Diazopyrazole-4-carboxamide is an effective inhibitor of xanthine oxidase (72MI1; 76MI1).

3. *Diazoimidazoles*

The 2-diazo-4-R-imidazoles ($R = H, CH_2COOH$) showed sufficient stability in neutral medium to be tested in binding experiments for the rat brain γ -aminobutyric acid (GABA) receptor (87JMC2222). They had an IC_{50} of $5.10^{-4} M$ and $7.10^{-5} M$, respectively, and they recognized the GABA receptor. Therefore they can be used as potential irreversible probes for this receptor.

4-Diazoimidazole-5-carboxylic acid esters have inhibitory activity in several different types of microorganisms. They can be used as sanitizing compounds (72USP3654257). In particular, methyl 4-diazoimidazole-5-carboxylate showed antimicrobial activity towards strains of microorganisms resistant to the action of certain known chemotherapeutic agents.

Although 4-diazoimidazole-5-carboxamide (known as Diazo-IC) is unstable in solution, there are reports of several types of biological activity, some of which have been reviewed (70JPS1533; 76MI1). Interpretation of biological results concerning Diazo-IC (especially the older ones) is complicated by the possibility of its conversion to 2-azahypoxanthine over a wide pH range (see Section III). For example, the compound with inhibitory activity against *Lactobacillus brevis* and *L. arabinosus* [51JBC(189)401] and *Mycobacterium tuberculosis* (63MI1) was probably a mixture of Diazo-IC and 2-azahypoxanthine. However, with suitable precautions in the screening tests, Diazo-IC has shown antimicrobial activity towards *B. subtilis* (70MI1), and completely inhibited *E. coli* *in vitro* without causing cell lysis (69MI2). This inhibitory effect can be abolished by the addition of cysteine. It was supposed that the major action of Diazo-IC in *E. coli* is to inhibit DNA synthesis by interfering with SH groups in biological systems. Another type of activity is represented by the potent inhibition of xanthine oxidase from cream and rat liver by the Diazo-IC and two thioazo derivatives prepared from it (69MI1). The extent of inhibition greatly decreased upon preincubation of these compounds in buffer (in which they are converted to 2-azahypoxanthine), and the activity of the Diazo-IC is suppressed by cysteamine, reduced glutathione, and cysteine in a process strongly catalyzed by metal ions. Possibly, Diazo-IC reacts covalently with vital thiol groups on the enzyme (73MI3). On the other hand, the inhibitory activity showed by Diazo-IC and the thioazo analogues against bovine kidney uricase has to be ascribed to 2-azahypoxanthine; the Diazo-IC acts only in a prodrug role (72MI1). Diazo-IC also showed positive ino- and chrono-tropic actions on isolated guinea pig atria, and this action is partially mediated by catecholamine release via interaction with tissue thiol groups (68MI2). Diazo-IC *in vitro* activated the

monoamineoxidase in rat tissue homogenates (70MI4) and induced the calcium-dependent release of 5-hydroxytryptamine (5-HT) from rabbit platelets (70MI3). This effect can be blocked by sulfhydryl compounds and inorganic pyrophosphate (71MI3). Diazo-IC could also potentiate hexobarbital hypnosis in mice by depressing hepatic metabolism of the drug (73MI1). Biological activities of Diazo-IC also include its influence on the reduction of body temperature (70MI5) and on flattening the electroencephalogram (EEG) in cats (67MI1). The antitumor activity shown by Diazo-IC is strictly connected with the antineoplastic activity of the triazenoimidazoles that can be prepared from Diazo-IC [see Sections III,B,5,b and V,B]. Diazo-IC inhibits the growth of solid tumor and Ehrlich ascites carcinoma in mice, (65MI2; 68MI1) and Walker 256 carcinoma in rats [61JOC2396]. But due to instability in solution, its potential usefulness as an antitumor agent is limited. The triazenoimidazoles instead could be a transport form of Diazo-IC, which can be generated from the imidazotriazenes upon exposure to light (62MI1; 78MI3). This theory, which had received some experimental support especially for the effects of imidazotriazenes on bacteria and tumor cells growing *in vitro* [see for example, the reviews on the activity of imidazotriazenes (70JPS1533; 76MI1)], has been abandoned after it was proved that Diazo-IC does not play a significant role in the *in vivo* antitumor action of imidazotriazenes (83MI1).

Imidazole-2-diazonium fluoroborate is an irreversible blocker of the phencyclidine binding site of the nicotinic cholinergic receptor, and it is only effective when the receptor is in a desensitized state, at variance with other aryldiazonium salts (85MI1).

4. *Diazotriazoles*

4-Diazo-1,2,3-triazole-5-carboxamide and 5-R derivatives (R = CN and carboxyhydrazide) showed > 50% inhibition of glycine-¹⁴C conversion to hypoxanthine by pigeon liver homogenates (68MI3). 4-Diazo-1,2,3-triazole-4-carboxamide, tested against leukemia (L1210), showed good activity increasing the life span of mice (66JMC733).

5. *Diazotetrazole*

Diazotetrazole interacts with enzymes. Thus, it decreased the dual specificity of carboxypeptidase A (67B700) and modified the activity of subtilisin BPN' (70MI2), papain and succinylpapain [75BBA(386)221], glutamate dehydrogenase (73MI2), fumarase (70N453), and mucor rennin (71ABC1398).

B. CHEMICAL USES

The chemical uses of diazoazoles can be divided into two classes. The first, actually very limited, involves the applications of the diazo compounds themselves. The second one implies the use of the diazoazoles as key intermediates for the synthesis of biologically interesting systems such as triazenes, azolo-triazines and azolo-tetrazines, and azo dyes, which are useful in photographic processes or in the textile industry. 2-Diazo-4,5-dicyanoimidazole has found application as an explosive (73USP3770764).

Diazotetrazole is used for spectrometric determination of histidine residues in several proteins (64BBA477). This reagent also allows the differentiation between free and heme-linked histidine residues (65MI3; 66MI1). Diazotetrazole is preferable to common diazonium compounds since histidine-bis-azo-1*H*-tetrazole, the reaction product spectrophotometrically determined, has a strong absorption band at 480 nm, while tyrosine-bis-azo-1*H*-tetrazole has a weaker band at a considerably longer wavelength, 550 nm, and the coloration due to the formation of bisazohistidine residues proceeds to completion before the bis coupling to tyrosine residues.

Taking advantage of the sensitivity to light shown by the diazoazoles allows them to be used in the photomechanical reproduction process to produce light sensitive layers or in photocopying processes as precursor of the azo dyes to be generated *in situ*.

In the lithographic process, the diazoazoles that are especially effective as light-sensitive agents are 3-diazopyrrole, 3-diazoindole, 3-diazoindazole, and 4-diazoimidazole derivatives. 3-Diazo and 4-diazopyrazoles and 4-diazotriazoles were also used for the same purpose but with less satisfactory results (59BRP816382). The diazo compound was applied to a metal or plastic surface. The coated plate was exposed to light under an original image to decompose the diazo compound at the unprotected parts. The decomposition products had in certain reagents a solubility different from that of the diazo compounds, therefore, the image could be developed by using these reagents. This image was highly ink and grease receptive and was used in offset reproduction. This process improved the lithographic reproduction since, in the earlier application, the plates, coated with diazonium salts, did not yield good images because of the poor stability of the diazo coated but unprocessed plates, especially in the absence of a colloid.

In the "dye line" photocopying process, paper or other base material is coated with a solution of a stable diazo compound and a coupling component and then dried. The diazoazoles used are 2-diazopyrrole, 3-diazopyrrole, 4-diazopyrazole, 3-diazoindazole, and 4-diazoimidazole deriv-

atives. The coupling components are usually phenol, β -naphthol, naphthol sulfonic acid, resorcinol, or β -hydroxynaphthoic acid (64BRP977326; 65BRP988221). The ratio of diazo compound and coupling component is 1:1 or, has an excess of diazo derivative if the coupling component has more than one coupling function. When the coated paper was exposed to ultraviolet light through a printed page, the diazo compounds decomposed at the part of the paper not protected by the print. The paper was then heated. Under these conditions, the diazo compound coupled with the coupling agent and the resultant dye reproduced the original print. The solution also contained other components to improve the qualities of the products. One of these components was the inhibitor that prevented premature coupling. In fact, the coupling reaction between the diazo and the phenol, though to a small extent, took place even at room temperature, causing general fogging of the image. A common inhibitor was oxalic acid. In an alternative process, the paper was coated with a solution containing the diazo compound and an acid phenolic coupler. A good acid phenolic coupler was β -hydroxynaphthoic acid. This "thermal" process represents an improvement of the dye line photocopying process in which the coupling reaction of stabilized diazonium salts was brought about by chemical methods.

Diazoazoles, pyrazoles, and imidazoles also found applications in the photographic processes as precursors of triazenes, which are useful as additives for developers in color photography (73GEP2253615). In the textile industry, azo dyes obtained from diazopyrazoles showed dyeing properties on cotton, wool, and nylon 6 (47USP2420791; 82MI1). Also, 1,3-ditetrazolyltriazene improved dyability and the feel of polyacrylonitrile filaments (58BRP796294).

Diazoazoles find wide application in the preparation of azolo-triazenes, which have shown several biological activities especially as antineoplastic agents. Triazenes are, in effect, latent diazo compounds because they decompose to give amino derivatives and diazonium salts so they can be employed as a carrier group for the diazo compounds (66JMC34).

Pyrazolyl-triazenes prepared from 3- and 4-diazopyrazoles were effective against lymphoid leukemia L1210 by increasing the survival time of the treated animals (70JPS1358; 71JMC1245; 71JPS554). 4-Triazolyl-triazenes also exhibited the same high antileukemia activity and significant but lower activity against Ca755, S180 and FVL tumor (66JMC733).

Generally, azolo-triazenes prepared from pyrazoles and triazoles are less toxic and more stable than the corresponding imidazo derivatives, probably because of the weaker basicity of the ring (69JMC545; 70JPS1358). However, the most important role in this area is played by the

triazenes obtained from 4-diazoimidazoles. Although they are less stable (70JPS1829), they are much more reactive, and in fact, one of them, Dacarbazine, is a well known antitumor drug.

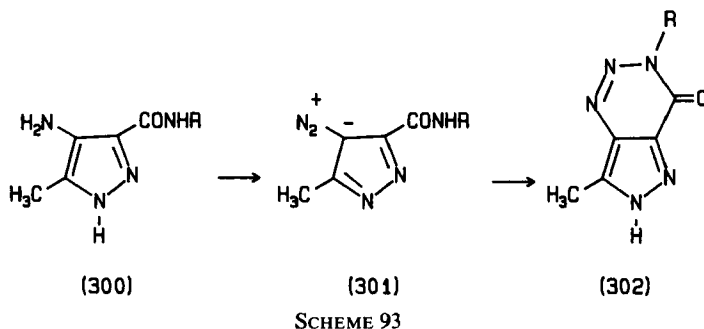
Several imidazo-triazenes showed inhibitory action in preventing the development of mouse leukemia L1210 (66N(L)208; 68JPS83; 75JPS177). Some also had a broad spectrum of antineoplastic activity, inhibiting the growth of sarcoma 180, adenocarcinoma 755, Walker carcinosoma 256 and Ehrlich carcinoma [68JPS1562; 76JAP(K)110564]. Among the dialkyl imidazo-triazenes, the dimethyl had the highest therapeutic effect. The antitumor activity of these compounds decreased with increasing length of the side chain, while the toxicity increased with chain length (68MI1). Both the antitumor activity and toxicity of the monoalkyl derivatives linearly decreased as the number of carbon atoms in the side chain increased. Imidazo-triazenes showed inhibitory activity against fungi and Gram-positive and Gram-negative bacteria (67JPS147; 72USP3654257; 73JAP00828).

2-Substituted-4-imidazolyl-triazenes found application as antiviral agents (73GEP2247065). Antibacterial, fungicidal and antixanthine oxidase activity was also shown by thioazoimidazoles [73JAP24392; 74JAP(K)48664]. Diazoazoles are used as key intermediates in the synthesis of substituted azolo-1,2,4-triazines, which showed *in vitro* antimicrobial activity (76JMC517). In particular, pyrazolo-triazines inhibited xanthine oxidase [68JPS1044], and imidazotriazines had inhibitory activity against lactic acid bacteria and yeast [51JBC(189)401].

Diazopyrazoles and imidazoles are useful intermediates in the synthesis of pyrazolo- and imidazolo-tetrazinones, which have shown anticancer activity, especially the mitozolomide that had curative activity against L1210 and P388 leukemia (84JMC196; 87JMC357). 4-Diazopyrazole are used in the synthesis of C-nucleoside antibiotics such as pyrazolomycin [81JCS(P1)2374].

VI. Appendix

This appendix contains a brief mention of reports that appeared in 1988. The diazotization of 3-amino-5-methylpyrazole and successive coupling with β -naphthol leading to azo dyes of type **188** was optimized (87URP1361145). Coupling of 3-diazopyrazoles and 3-diazoindazole with 3-terbutoxy-1,6-methano[10]annulene gave the corresponding azo dyes, which, by elimination of *t*-butanol, cyclized to the methano-bridged triazines (88CB1359).



Diazotized 4-arylo-3,5-pyrazolediamines gave pyrazolo[1,5-*c*]triazines of type **197** by direct coupling of the diazo compound, generated in situ, with activated methylene compounds (88LA819). Diazotization of amide-*N*-substituted 4-amino-3-methyl-pyrazole-5-carboxamides **300** gave either the 4-diazopyrazoles **301** or the pyrazolo-triazines **302**, depending on the nature of the substituent in the amide function (Scheme 93). Electron-withdrawing groups allow the isolation of the diazo compound **301** (88S78). 3-Diazopyrrole-4-carboxamides could not be isolated by diazotization of the corresponding 3-amino-pyrroles even in acetic acid or in buffered conditions. Pyrrolo[3,4-*d*]triazines were always isolated (88UP3).

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Organocobalt-Catalyzed Synthesis of Pyridines

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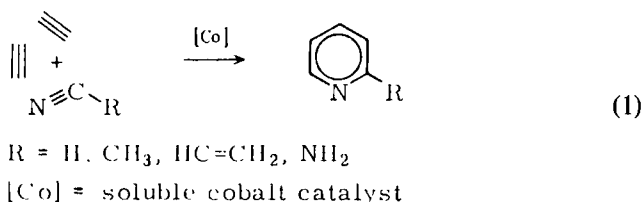
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I. Introduction

There is ample information available on the metal-catalyzed transformation of olefins and alkynes into products of synthetic or industrial value (82MI1). Because of the inherent sensitivity of most organometallic catalysts to substrates containing polar hetero atoms, their use in the synthesis of heterocyclic compounds appears to be comparatively limited. A first review by Bird [73JOM(47)281] covers the literature up to 1971, Davidson and Preston have compiled a synthetic methodology up to the end of 1979 [79AHC(30)321], and in 1984, Hegedus (85MI2) presented a survey on palladium-promoted syntheses of indole derivatives. The cobalt-catalyzed

synthesis of pyridine and its derivatives was summarized in 1984 from the viewpoint of applied organometallic chemistry (84MI2). This review is concerned particularly with the use of this reaction as a tool in the synthesis of heterocycles.

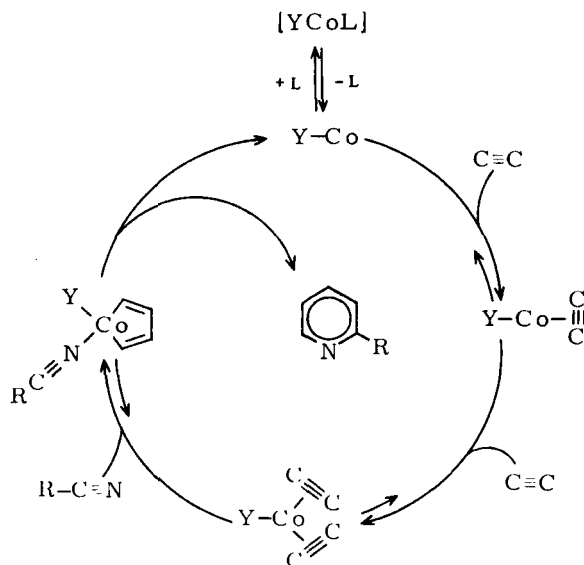
Pyridine and its derivatives are technically-important fine chemicals. Their isolation from coal tar is decreasing, whereas their manufacture by synthetic methods has increased rapidly. The classical pathways to pyridine have been discussed by Abramovitch (74HC14-1-4). Many of them rely on the reaction of aldehydes or ketones with ammonia in the vapor phase. However, the condensation processes used suffer from unsatisfactory selectivity. Using soluble organocobalt catalysts of the type [YCoL] allows pyridine and a wide range of 2-substituted derivatives to be prepared selectively and in one step from acetylene and the appropriate cyano compound [Eq.(1)].



An important aspect of the reaction came with the realization that the organo group Y remains attached to the cobalt throughout the catalytic cycle [Scheme 1]. This opened up the possibility of optimizing the catalyst by varying the controlling ligand Y.

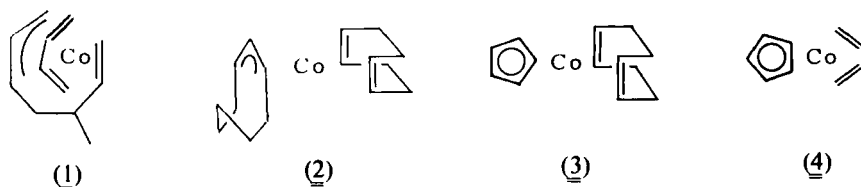
Remarkably, the catalytic cycle is not controlled by the presence of phosphine ligands, but it is controlled by the organo group Y at the cobalt: the neutral ligand L is displaced by the substrates in the initial step. Oxidative addition of two acetylenes results in a cobaltacycle that reacts with the nitrile to give the pyridine derivative with regeneration of the active [YCo] species.

The basic cyclotrimerization reaction of Eq.(1) was first observed in 1876 by Sir William Ramsey (1876MI1; 1877MI1; 1885MI1; 13MI1) who led acetylene and hydrogen cyanide through a red-hot iron tube and obtained small amounts of pyridine. In 1973 Yamazaki (73TL3383) first reported a homogeneous catalytic [2 + 2 + 2]-cycloaddition of alkynes and nitriles, using a phosphine-stabilized cobalt(III) complex. At the same time, we (74GEP2416295, 74S575; 75USP4006149) observed the catalyzed cocyclization [Eq.(1)] on cobalt catalysts prepared *in situ*, as well as on



SCHEME 1. Synthesis of substituted pyridines with complexes of type $[YCoL]$. Y is the controlling ligand; L is the neutral ligand.

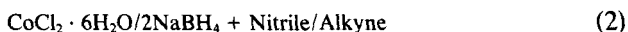
easily accessible phosphine-free organocobalt-diolefin complexes of the type (1)–(4).



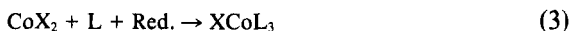
The substituents on the alkyne and the cyano components can be widely varied so that we have been able to develop the basic reaction of Eq.(1) into a general synthetic method for preparing pyridines (see Section III). We have concentrated on the development of highly reactive organocobalt(I) complexes and have tested a number of catalyst complexes under standard conditions. Both the influence of the “controlling ligand” Y and the “neutral ligand” L on the catalytic turnover number (TON) have been determined. The final step involves the optimization of the reaction conditions.

II. Survey of Catalysts

With the exceptions of a few rhodium systems (see following), the catalytic pyridine-synthesis relies exclusively on cobalt as the active metal. The reaction can be carried out advantageously in a one-pot reaction by generating the cobalt catalysts *in situ* [Eq.(2)] (74GEP2416295, 74S575; 75USP4006149).



Prior to the initiation of catalysis, a small amount of a suitable cobalt salt is dissolved or suspended in the substrate mixture. In the activation step, the anions are removed from the cobalt with metals of the first to third main groups or their hydrido or alkyl compounds. The coordination sites at the cobalt are occupied by substrate molecules. The *in situ* system [Eq.(2)] has proved most valuable in the laboratory since the cobalt salt can be used in hydrated form, and the use of inert atmosphere or additional stabilizing ligand is unnecessary. Halogenocobalt(I) complexes of the type $[\text{XCoL}_3]$ are easily accessible [69MI1; 81JOM(205)239] and showed a moderate activity in the synthesis of 2-alkylpyridines (85UP1) [Eq.(3)],



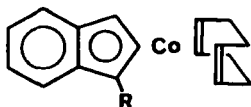
where $\text{X} = \text{Cl}, \text{Br}, \text{I}$; $\text{Red.} = \text{NaBH}_4, \text{Zn}$; and $\text{L} = \text{P}(\text{C}_6\text{H}_5)_3, \text{P}(\text{C}_6\text{H}_5)_2(\text{C}_4\text{H}_9), \text{P}(\text{C}_6\text{H}_5)_2(\text{C}_7\text{H}_7), \text{P}(\text{OEt})_3, \text{P}(\text{OC}_3\text{H}_7)_3$.

Organocobalt-half-sandwich compounds generally exhibit high catalytic activities in the pyridine synthesis. The metal atom in the catalysts involving an η^3 -allylcobalt species (**5**) have 12 valence electrons. The classical example is (**6**) [67MI1, 67TH1; 68JCS(A)2630; 69CC1293; 71JOM(30)407], but recent work (85TH1; 88TH1) has also made a number of allylcobalt-arene systems available (Scheme 2).

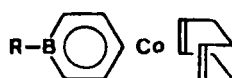
In the case of the η^5 -cyclopentadienyl (cp) (**7**) and η^5 -indenylcobalt-catalysts (**8**), the catalytic circle involves a 14-electron moiety. Modification of the basic system by additional substituents, R, having electron-donating or withdrawing effects on the cp ring results in marked changes in catalyst activity. In addition, η^6 -borininato ligands may be used as 6 π -electron ligands for cobalt [78JOM(160)17; 82GEP310550; 83EUP101246] (**9**).



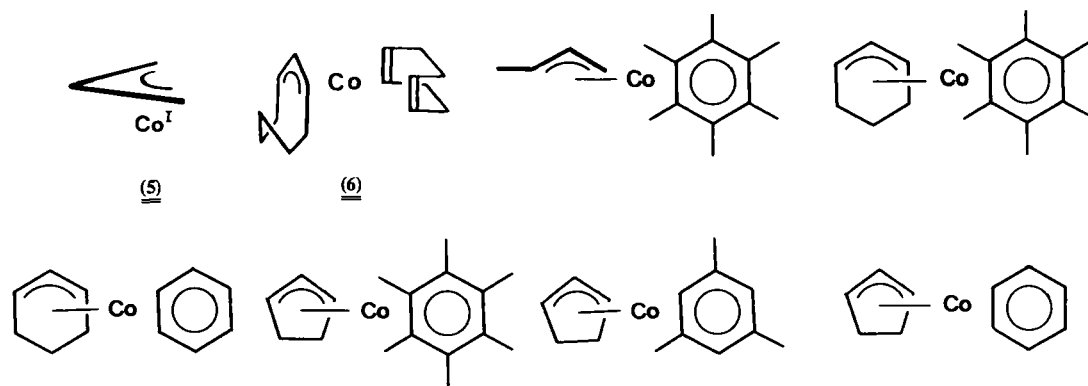
(7)



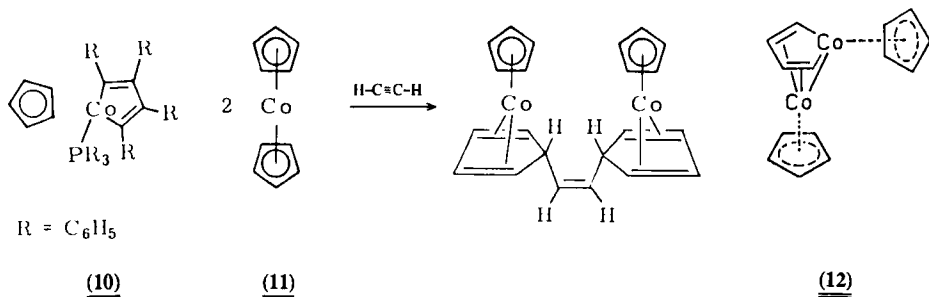
(8)



(9)



SCHEME 2

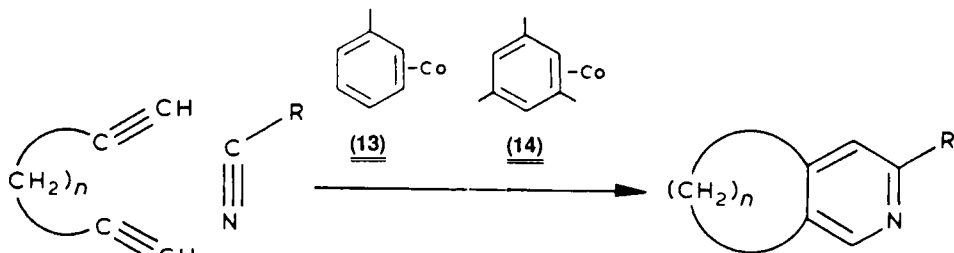


SCHEME 3

Yamazaki's complex (10) contains two acetylene molecules linked together to form a five-membered metallacycle. However, the Japanese authors report the synthesis of (10) to be difficult, and subsequently they turned to cobaltocene (11) as a catalyst (76S26). Under the reaction conditions, cobaltocene reacts with acetylene to give the η^4 -diene complex of cpCo , which is the true catalyst. The Lonza A. G. devoted their efforts towards developing a technically feasible process using cobaltocene and its analogues in the synthesis of 2-vinylpyridine (76GEP2615309). The binuclear cpCo system (12) (73MI1) is to be regarded as a special case of the $\text{cpCo}(\text{diene})$ -type catalyst (Scheme 3).

Arene-solvated cobalt atoms (13) and (14), obtained by reacting Co vapor and arenes, have been found by Italian workers to promote the conversion of α,ω -dialkynes and nitriles to alkynyl-substituted pyridines [87JOM(326)C33] (Scheme 4).

We (79TH1; 81GEP3117363; 84USP4588815) and others (87MI1) have studied acetylacetonato and η^5 - cp -rhodium complexes as catalysts in the pyridine formation [Eq.(1)]. Resin-attached cp -rhodium complexes are also active in the cocyclization of alkynes and nitriles, and the activity is



SCHEME 4

markedly dependent on the nature of the rhodium-bonded ligands in the same way as observed for cobalt (87MI2). However, the rhodium catalysts are inferior to the analogous cobalt systems.

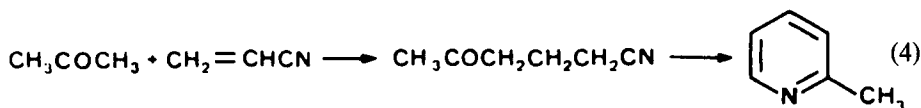
Comparison of the different types of cobalt catalysts shows that the *in situ* system [Eq.(2)] is most accessible while the Rcp-, R(ind)-, and borinato ligands having electron-withdrawing substituents are the most active. The difference between the $14e^-$ and the $12e^-$ core complexes makes itself apparent in the chemoselectivity of the reaction. Catalysts containing a 14-electron core favor pyridine formation, whereas those containing a 12-electron core (i.e., the η^3 -allylcobalt systems) favor the formation of benzene derivatives by cyclotrimerization of the alkynes. For example, in the reaction of propyne and propionitrile at 140°C in the presence of a 12-electron system (**5**), a 2 : 1 ratio of benzene to pyridine product is formed, whereas a catalyst containing the cpCo moiety (a 14-electron system) leads (under identical conditions) to the predominant formation of pyridine derivatives (84HCA1616).

III. Applications of Cobalt-Catalyzed Pyridine Synthesis

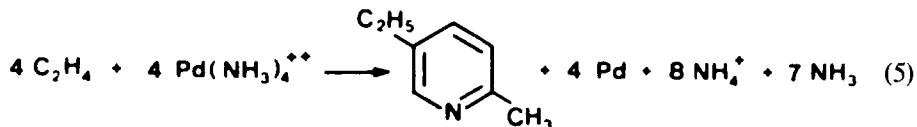
The cobalt-catalyzed pyridine synthesis is the only known one-step process for the selective preparation of the industrially significant 2-substituted-pyridine derivatives. Moreover, the method is applicable to a broad variety of substituted alkynes and nitriles, thereby giving access to a whole range of pyridine derivatives having 1,2,3 or 5 substituents in the ring. Selected examples follow and are compared to the prior state of the art.

A. 2-METHYLPYRIDINE (α -PICOLINE)

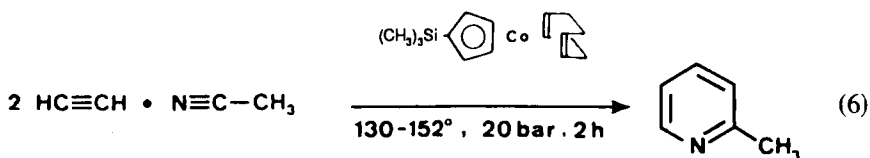
A two-step process for the production of 2-methylpyridine (2-picoline) has been commercialized by the Dutch Stats Mijen in which acrylonitrile is reacted with a large excess of acetone [Eq.(4)] (73BRP1304155, 73USP3780082; 74BRP1378464; 77MI2). Initially a monocyanoethylation product is formed in the liquid phase in a process catalyzed by a primary amine and a weak acid and which occurs at 180°C and 2.1 MPa. The ring closure to 2-methylpyridine is catalyzed by a Pd-containing contact and is conducted in the vapor phase [Eq.(4)].



Nippon Steel has developed an interesting liquid-phase process for producing 2-methylpyridine from ethylene and ammonia (74MI1; 81MI2, 81MI3). The catalyst is reminiscent of the well-known Wacker process, *viz.* $\text{Pd}^{2+}/\text{Cu}^{2+}$ redox system [Eq.(5)].



The TON, i.e., moles of product per mol of catalyst, and the productivity (PROD), i.e., kg of product per g of metal, are the key numbers for evaluating a given catalyst. Catalyst screening has revealed that the trimethylsilyl-substituted cp-group is the preferred system for the cocyclization of acetylene and acetonitrile to give 2-methylpyridine (80EUP009685; 81USP4266061) [Eq.(6)].

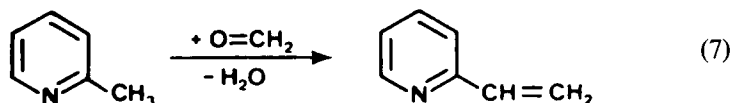


TON: 4088

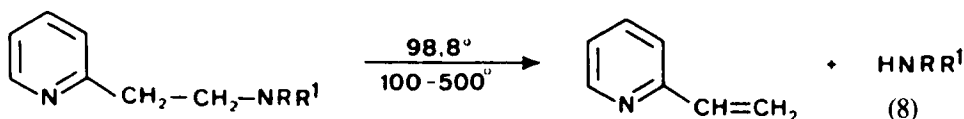
PROD: 6.445

Since two acetylene molecules are coordinated to the cobalt in the rate-determining step (79TH2), the catalysis has to be performed with a high, stationary alkyne concentration in solution. Fortunately, nitriles turned out to be good solvents for acetylene, and apparently the nitrile triple bond prevents the decomposition of acetylene. By using the nitrile without additional solvents, acetylene can be safely worked with at up to 6.9 MPa without dilution by inert gases. The acetylene may be added in one batch to the nitrile and the dissolved catalyst at 20–25°C and 1.7 MPa. The resulting solutions contain about 40% acetylene by weight. During the reaction (4 hrs at 130–200°C), a maximum pressure of 6.0 MPa may be reached which then slowly drops as the acetylene is consumed. Alternatively, a constant acetylene pressure of 2.0 MPa is maintained with the help of a compressor connected to the autoclave (see Section IV). The yields can be as high as 80% based on 25% nitrile conversion, and the product can be easily separated from the reaction mixture. The pyridine/benzene selectivity reaches 21/1. Further experimental data are available (84MI3).

The total consumption of 2-methylpyridine (α -picoline) in 1980 has been estimated at ~12,000 tons [81CI(L)23]. Half is produced for the U.S. market, whereas the demand in both Western Europe and Japan lies between 2000 and 2500 tons per annum. A significant outlet for 2-methylpyridine is in the production of 2-chloro-6-(trichloromethyl)pyridine, which is used as a nitrification inhibitor in agricultural chemistry and in the manufacture of the defoliant 4-amino-2,5,6-trichloropicolinic acid. The major commercial outlet for 2-methylpyridine is, however, its use as a starting material for the production of 2-vinylpyridine [Eq.(7)].

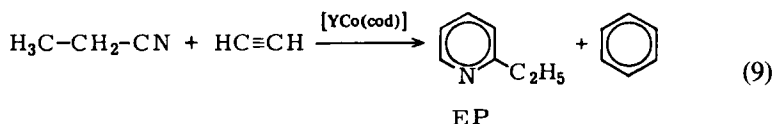


The total yield of 2-vinylpyridine formed from 2-methylpyridine can be as high as 90%. 2-Vinylpyridine may also be obtained in almost quantitative yields by heating 2-alkylaminopyridine derivatives (which are directly available by cobalt catalysis) with a supported (e.g., Al_2O_3) alkali metal hydroxide [Eq.(8): $\text{R} = \text{R}^1 = \text{alkyl}$, cyloalkyl, etc., $\text{RR}^1\text{N} = \text{heterocycle}$] (76SZP14399; 78MI1).



B. 2-ETHYLPYRIDINE

In order to obtain maximum catalytic TON, pyridine yields, nitrile conversions, as well as high pyridine/benzene ratios in the product, more than 60 [YCoL] complexes were systematically investigated for the catalytic cotrimerization of propionitrile and acetylene [Eq.(9)] [85AG264, 85AG(E)248].



The catalytic screening was carried out with high-pressure acetylene in a batch reactor (see Section IV). The range of results are shown in Table I.

TABLE I
 THE SYNTHESIS OF 2-ETHYLPYRIDINE (EP) ON [YCoL] ACCORDING TO EQ. (9)^a

Catalyst 0.14 mmol ^b	Acetylene (g) ^c	T °C ^d	Nitrile yield	EP benzene	EP ^e	TON _{Py}
(Ph ₄ C ₅ H)Co(cod)	62	110-165	25.7	91.8	7.9	6946
(CH ₃ OCO—C ₅ H ₄)— Co(cod)	60	100-160	41.6	94.5	6.2	6060
(C ₆ H ₅ CO—C ₅ H ₄)— Co(cod)	93	95-185	40.0	97.7	4.6	4612
[1,2—(Me ₃ Si) ₂ C ₅ H ₃]— Co(cod)	48	120-165	17.4	93.5	10.7	2611
(Me ₅ C ₅)Co(cod)	29	up to 185	1.9	15.4	2.1	50

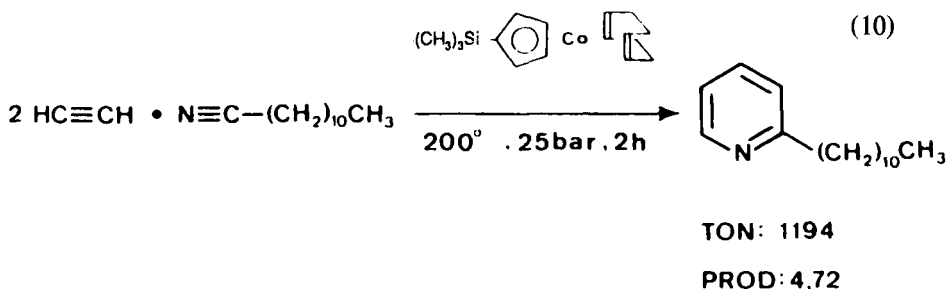
^a The best results are boldface.^b In 150 ml propionitrile.^c Acetylene reservoir at 20°C in 150 ml propionitrile.^d Reaction temperature range.^e Based on 2 hrs reaction time.

The TON values vary between 50 and 7000 catalytic cycles per cobalt, i.e., by a factor of 140. [YCo] systems having electron-withdrawing groups on the ligand Y yield maximal TON, while alkyl substituents lower the TON drastically. Nitrile conversions of 2 to 42% are achieved within 2 hrs. Catalysts that achieve conversions in excess of 20% can be regarded as preparatively useful. The 2-ethylpyridine yield (based on nitrile conversion) varies between 15 and 98%. Best chemoselectivity is found for the 1,2-bis(trimethylsilyl)cyclopentadienylcobalt catalyst, which gives ~11 moles of pyridine derivative per mole of benzene. Comparison of the TON values of the [YCoL] complexes having various neutral ligands confirms that strongly complexing ligands such as triphenylphosphine or CO hinder the generation of the active species. The maximum amount of acetylene that can be introduced initially at room temperature (the maximum safety limit at the reaction temperature is 6.9 MPa) is of importance for the preparative success of the cobalt-catalyzed pyridine formation. Highly reactive catalysis quickly use up the acetylene reservoir so that the pressure stabilizes after reaching a maximum of 4.0–6.5 MPa and rapidly sinks at the end of the reaction. When using [YCo] systems of low reactivity, only small amounts of acetylene in the reservoir are used so as not to exceed the safety limit at 6.9 MPa. The temperature control is also of importance in the cobalt-catalyzed pyridine synthesis. The thermal stabilities of the industrial [YCo]-systems vary widely; the trimethylsilyl-cpCo-system remains uncharged at 200°C, whereas the indenyl-Co-system (**8**) decomposes at 150°C under the catalysis conditions. In order to make full

preparative use of the activity, the amount of acetylene and the temperature control have to be carefully optimized. Even minor deviations from the optimal combination of the parameters can lead to fluctuations of 1000 in the TON for the same catalyst.

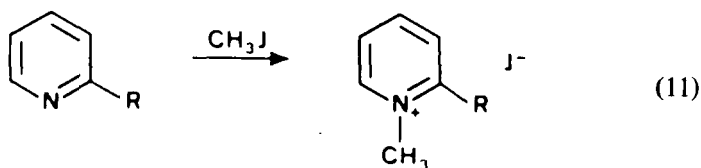
C. ADDITIONAL 2-ALKYLPYRIDINES

2-Undecylpyridine can be prepared in an analogous way from acetylene and undecylcyanide. The preferred catalyst is a trimethylsilyl-cpCo-system [Eq.(10)].



The product is formed in up to a 94% yield and can, moreover, be easily separated from the reaction mixture. Conventional alkylation reactions (56GEP952807, 56MI1) have yields that lie between 22 and 54%, suggesting that the cobalt-catalyzed procedure might be an attractive pathway for large scale production.

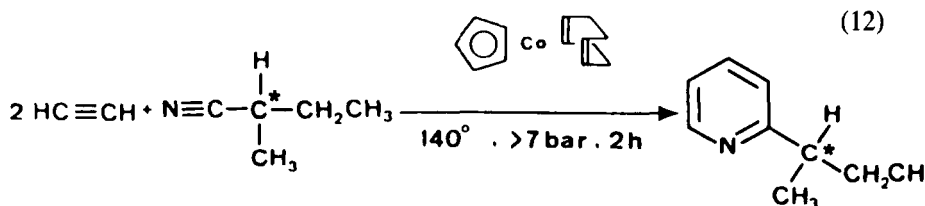
The hydrochlorides and methiodides of a number of 2-alkylpyridines [Eq.(11), where $\text{R} = \text{C}_n\text{H}_{2n+1}$] have been examined for their effect on aqueous surface tension and for their antibacterial properties.



Maximum activity in both cases is found with the salts of 2-pentadecyl pyridine (51JCS1263). 2-Alkylpyridines having C_{10} - C_{18} -alkyl chains have attracted some industrial interest as starting materials for further derivation; experimental details may be found in Bönnemann and Brijoux (84MI4).

C. Botteghi [75JOC2987; 82JOM(229)93] has applied the cobalt-

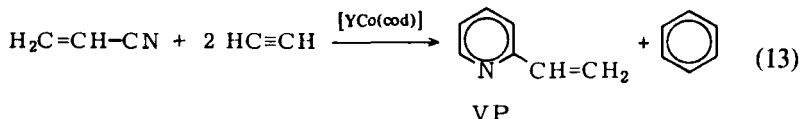
catalyzed reaction in a unique synthesis of optically active 2-substituted pyridines [Eq.(12)] starting from optically pure cyanides.



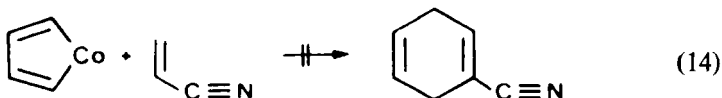
During cyclization with acetylene, the chiral center is maintained. This reaction has recently been extended to the synthesis of bipyridyl compounds having optically active substituents (75PC1) and provides access to chiral ligands of potential interest in transition-metal-catalyzed asymmetric catalysis.

D. 2-VINYLPYRIDINE

Probably the most interesting application from the industrial point of view is the cobalt-catalyzed one-step synthesis of 2-vinylpyridine [Eq.(13)].

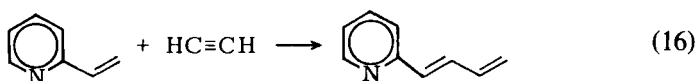


The most important outlet for 2-vinylpyridine (VP) is in the manufacture of copolymers for use as tire-cord binders. The tire cord is treated first with a resorcinol formaldehyde polymer and then with a terpolymer made from 15% 2-vinylpyridine, styrene, and butadiene. This treatment gives the close bonding of tire cord to rubber essential in the production of tires (77MI1). As a result, the market for automobiles dictates the production. 2-Vinylpyridine is also used as an additive in the drying of acrylic fibers: 1–5% of added copolymerized 2-vinylpyridine serves as the reactive site for the dye. This valuable, fine chemical can be manufactured using equal amounts by weight of acetylene and acrylonitrile, both of which are comparatively inexpensive. The VP synthesis [Eq.(13)] must be carried out below 130°–140°C, since acrylonitrile and the product undergo thermal polymerization (82MI2). Remarkably, a pseudo Diels–Alder reaction [Eq.(14)] involving the C,C double bond of the acrylonitrile is not observed.



The [YCo] systems catalyze this reaction only above 130°C, and hence, the reaction must be carried out in dilute benzene or toluene solutions to keep the TON values below ~500. Only very active catalysts can be used for the reaction of Eq.(13) when carried out in pure acrylonitrile. Every cobalt catalyst sufficiently active below 125°C was tested in a batch reactor. A solution of the catalyst in pure acrylonitrile was saturated with acetylene at ~2.0 MPa and then heated to 130°C (for experimental procedures, see 84MI5). The TON values after 2 hrs are summarized in Table II. The best results were obtained with the η^6 -phenylborininato complex (9), which produced 2.78 kg VP/g Co.

In the presence of this catalyst, the catalytic vinylation reactions of Eqs.(15) and (16) are largely suppressed.



In the presence of all the other catalysts shown in Table II, acrylonitrile and VP react further to give appreciable amounts of activated olefins which can compete with the acetylene for cobalt coordination sites and therefore act as a catalyst poison.

TABLE II
SYNTHESIS OF 2-VINYLPYRIDINE (VP) ON [YCoL] (T < 130°C)

Catalyst 0.14 mmol ^a	Acetylene (g) ^b	Nitrile yield	VP benzene	VP ^c	TON _{Py}
(1-C ₆ H ₅ -C ₅ H ₅ B)Co(cod)	58	14.2	61.6	6.6	2164
(Ph ₄ C ₅ H)Co(cod)	57	15.5	73.7	8.5	1624
(CH ₃ OCO-C ₅ H ₄)Co(cod)	58	14.9	69.2	5.4	1513
(C ₂ H ₅ CO-C ₅ H ₄)Co(cod)	64	15.1	80.4	6.1	1421
(CH ₃ CO-C ₅ H ₄)Co(cod)	58	12.9	81.1	5.8	1345
(C ₆ H ₅ CO-C ₅ H ₄)Co(cod)	67	11.9	78.9	6.0	1286

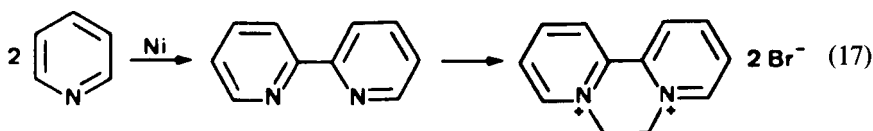
^a In 150 ml acrylonitrile.

^b Acetylene reservoir at 20°C in 150 ml acrylonitrile.

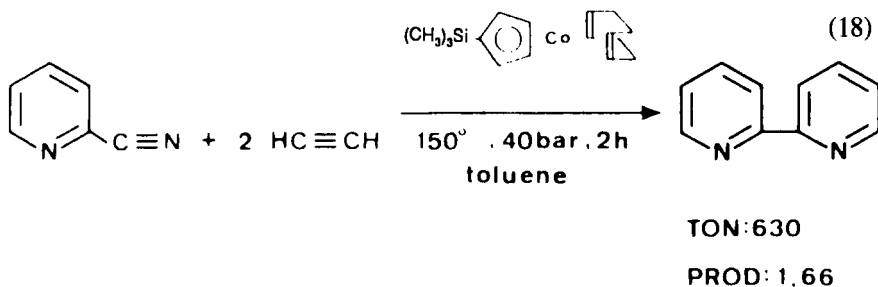
^c Based on 2 hrs reaction time.

E. CATALYTIC SYNTHESIS OF BIPYRIDINES

The classical route for producing 2,2'-dipyridyl consists in the dehydrodimerization of pyridine on Raney-Ni using a process developed by the Imperial Chemical Industries [63AHC(2)179; 68CI(L)49, 80MI4]. 2,2'-Bipyridyl reacts with ethylene bromide to give 1,1'-ethylene-2,2'-bipyridylum bromide (diquat). The production of one ton of the diquat (which is widely used as a herbicide) requires 1.2 tons of pyridine [Eq.(17)].



The cobalt-catalyzed synthesis enables 2,2'-dipyridyl to be prepared directly from 2-cyanopyridine and acetylene in a 72% yield with a cyanopyridine conversion of 21%. The pyridine : benzene ratio in the product is 2.7 : 1 [Eq.(18)].



This reaction has to be carried out in benzene or toluene, and a comparatively high acetylene pressure has to be maintained in order to achieve a sufficiently high, stationary alkyne concentration in the solution (for experimental details, see 84MI6). Polynuclear pyridine derivatives can also be synthesized, in high yields, using cobalt catalysts. Up to 350 catalytic cycles have been achieved (75S600). Starting from the readily available pyridinecarbonitriles, reaction with terminal alkynes leads to the bipyridines [Eq.(19)]. Use of acetylene as the alkyne component gives the respective parent bipyridine. Substituted alkynes give two positional isomers, of which type (15) usually predominates. The bipyridines (15) and (16) bearing different substituents on the two rings, which are inaccessible

TABLE III
BIPYRIDINE DERIVATIVES (13) AND (14)^a

$$\text{X-CN} + 2 \text{ R-C}\equiv\text{CH} \xrightarrow{[\text{Co}]} \text{Pyridine (13)} + \text{Pyridine (14)}$$

X	R	Isomeric ratio ^b		Major fraction b.p. ^c		
		(13):(14)	% Yield	(°C/hPa)	n _D ²⁰	M ⁺ (m/e) ^d
2-Pyridyl	H		72	273/1013		156
	CH ₃	72 : 28	69	122/10 ⁻³	1.589	184
	C ₆ H ₅	60 : 31	74	120/10 ⁻⁴		308
3-pyridyl	H		72	286/1013		156
	CH ₃	62 : 38	74	123/10 ⁻³	1.589	184
4-Pyridyl	H		73	281/1013		156
	CH ₃	54 : 46	70	125/10 ⁻³	1.589	184

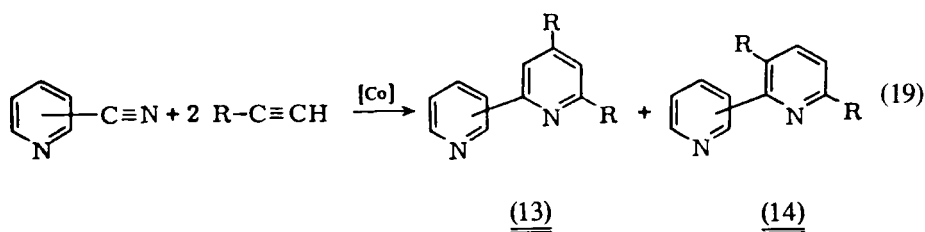
^a Catalyst, cpCo(cod); reaction temperature, 120°–130°C 20% conversion; work up by distillation.

^b Determined by ¹H-NMR spectroscopy.

^c b.p., boiling point.

^d m/e, Mass-to-charge ratio.

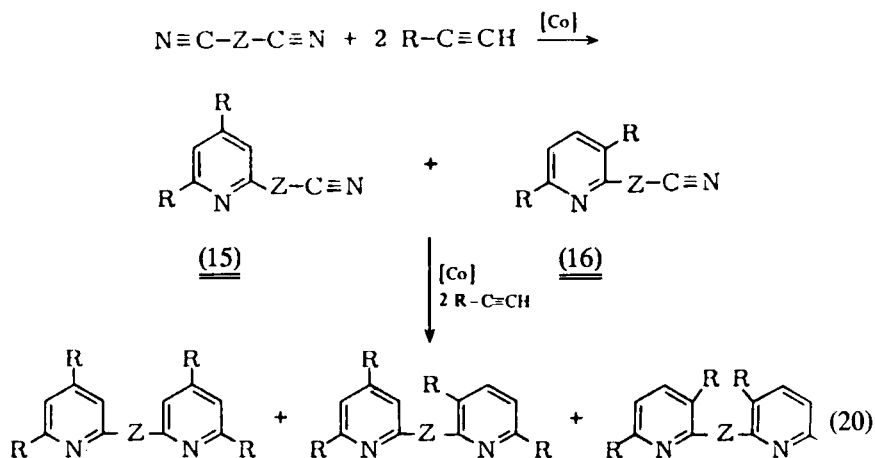
by classical methods, could be of interest for the synthesis of transition-metal bipyridine complexes. Some typical examples are shown in Table III.



F. CO-OLIGOMERS OF α,ω -DINITRILES AND ALKYNES

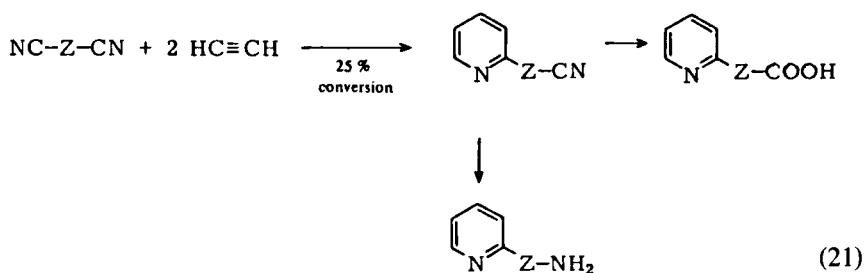
The cobalt-catalyzed synthesis is also applicable to bifunctional nitriles [Eq.(20)]. The starting materials containing different bridging groups afford the bis(2-pyridyl) derivatives. The reaction proceeds stepwise: in the

first step, the monopyridyl derivatives are formed; this is followed by reaction of the cyano group with further alkyne.



The method can be used to prepare relatively inaccessible or unknown oligomethylenepyridines in good yield; ~450 cycles are achieved per cobalt atom (Table IV).

If the catalytic reaction is interrupted after ~25% dinitrile consumption, then monopyridyl derivatives may be obtained without difficulty on a preparative scale [Eq.(21), Table V].



G. DIALKYL- AND TRIALKYLPYRIDINES

The reaction of monosubstituted alkynes with nitriles gives a mixture of isomeric trialkylpyridines (collidines) [Eq.(22)].

They can be prepared with high catalyst TONs at 130°C using cpCo(cod) (Table VI).

TABLE IV
2,2'-OLIGOMETHYLENEDIPYRIDINES AND 2,2'-(1,4-PHENYLENE) dipyridine^a

Z	R	% Yield	Major fraction b.p. ^c (°C/hPa)	n _D ²⁰	M ⁺ (m/e) ^d
—CH ₂ —	CH ₃	72 ^b	90/10 ⁻³		170
	C ₆ H ₅	70 ^b	160/10 ⁻⁴		474
—(CH ₂) ₂ —	H	97	105–110/0.6	1.578	184
	CH ₃	94	143–146/0.1		240
	C ₂ H ₅	83	170/10 ⁻⁴		488
—(CH ₂) ₃ —	H	92	135/33		198
	CH ₃	96	155/0.1		254
—(CH ₂) ₄ —	H	98	125/0.25		212
	CH ₃	90	160/0.1		268
	C ₆ H ₅	86	178/10 ⁻⁴		516
—(CH ₂) ₅ —	H	92	126/10 ⁻³		226
	C ₆ H ₅	81	189/10 ⁻⁴		530
—(CH ₂) ₆ —	H	97	128/10 ⁻³		240
	CH ₃	92	137/10 ⁻³		296
—(CH ₂) ₇ —	H	92	128/10 ⁻³	1.536	254
	CH ₃	94	160/10 ⁻³		310
	C ₆ H ₅	79	230/10 ⁻⁴		558
—(CH ₂) ₈ —	H	90	100/10 ⁻⁴		268
	CH ₃	96	122/10 ⁻⁴		324
1,4—C ₆ H ₄	H	94	230/2.5 · 10 ⁻³		232

^a Catalyst, cpCo(cod); reaction temperature, 140–150°C; almost complete conversion; work up by distillation.

^b 4-Amino-2,6-bis(cyanomethyl)-5-Pyrimidinecarbonitrile is formed as a byproduct in a yield of preparative interest.

^c b.p., Boiling point.

^d m/e, Mass-to-charge ratio.

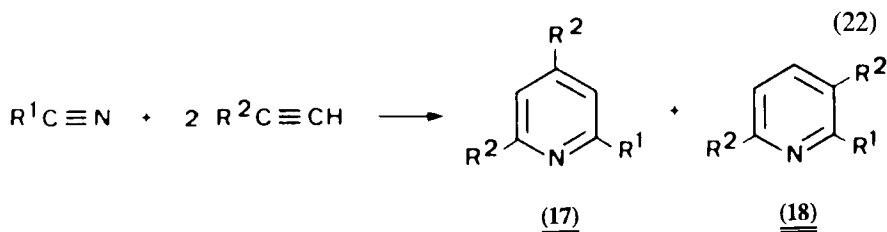


TABLE V
 ω -(2-PYRIDYL)ALKANONITRILES (15) AND (16)^a

Z	R	Isomeric ratio ^b		% Yield	Major fraction b.p. ^c °C/hPa	n _D ²⁰	M ⁺ (m/e) ^d
		(15)	(16)				
—(CH ₂) ₂ —	CH ₃	72	28	79	96–98/2.5	1.518	160
—(CH ₂) ₃ —	CH ₃	70	30	81	95–97/1	1.519	174
—(CH ₂) ₄ —	CH ₃	71	29	89	135–138/0.5	1.489	188
—(CH ₂) ₆ —	CH ₃	72	28	83	142–145/0.6	1.484	216
—(CH ₂) ₈ —	CH ₃	77	23	84	150–152/0.25	1.463	244
—CH ₂ —	C ₆ H ₅	69	31	59	170–185/10 ⁻⁴		270
—(CH ₂) ₄ —	C ₆ H ₅	72	28	68	177–196/10 ⁻⁴		312
—CH ₂ —CH=CH—CH ₂ —	CH ₃	74	26	78	90–99/10 ⁻⁴		186
1,4—C ₆ H ₄	CH ₃	62	38	85	110–120/10 ⁻⁴		208

^a Obtained according to Eq. (20) At 25% dinitrile conversion; catalyst, cpCo(cod); reaction temperature, 80–90°C; work up by distillation.

^b Determined by ¹H-NMR spectroscopy.

^c b.p., Boiling point of mixture of isomers.

^d m/e, Mass-to-charge ratio.

 TABLE VI
 TRISUBSTITUTED PYRIDINES (17) AND (18) OBTAINED ACCORDING TO EQ. (22)^a

R ¹	R ²	Isomeric ratio ^b		Separation or identification	% Yield	b.p.[°C/hPa] ^d	m.p. (°C) ^e	M ⁺ (m/e) ^f
		(17)	(18)					
CH ₃	CH ₃	61	39	GC	71	174–179/1013		121
CH ₃	n-C ₅ H ₁₁	69	31	GC	58	84–96/10 ⁻⁴		233
CH ₃	C ₆ H ₅	80	20	¹ H-NMR	62	170–190/10 ⁻⁴	56	245
C ₂ H ₅	CH ₃	75	25	GC	84	69–73/18		135
				¹ H-NMR				
C ₂ H ₅	C ₆ H ₅	65	35	¹ H-NMR	55	180–200/10 ⁻⁴		259
n-C ₅ H ₁₁	CH ₃	60	40	GC	62	47–61/10 ⁻⁴		
CH=CH ₂	CH ₃	71	29	¹ H-NMR	85	81/16		133
C ₆ H ₅	CH ₃	68	32	GC	54	58–95/10 ⁻⁴		183
C ₆ H ₅	C ₆ H ₅	77	23	GC	51		138	307

^a Catalyst, cpCo(cod); reaction temperature, ~130°C; work up by distillation.

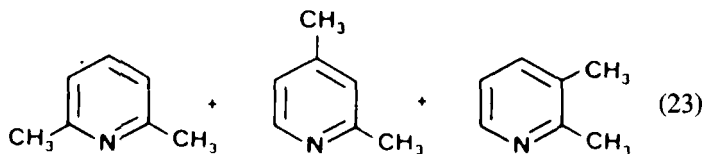
^b The isomeric ratio was determined (¹H-NMR) from the intensity ratio of the signals characteristic for each of the structures.

^c Based on reacted alkyne, not optimized.

^d Boiling point of mixture of isomers.

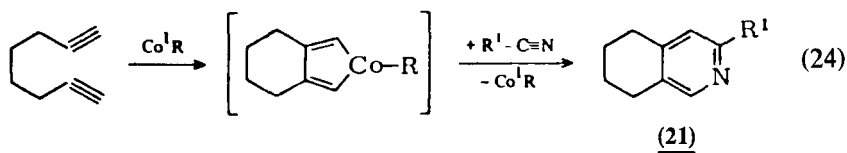
^e Melting point of mixture of isomers; purification by acid–base separation.

The catalytic reaction may also be carried out with two different alkynes. For example, the cycloaddition of acetylene and propyne with acetonitrile yields a mixture of dimethylpyridine (lutidines) in addition to 2-methylpyridine and the isomeric collidines. The cycloaddition [Eq.(23)] is not selective and appears to occur statistically.

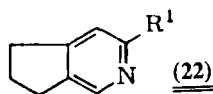


H. CO-OLIGOMERS OF α,ω -DIYNES AND NITRILES

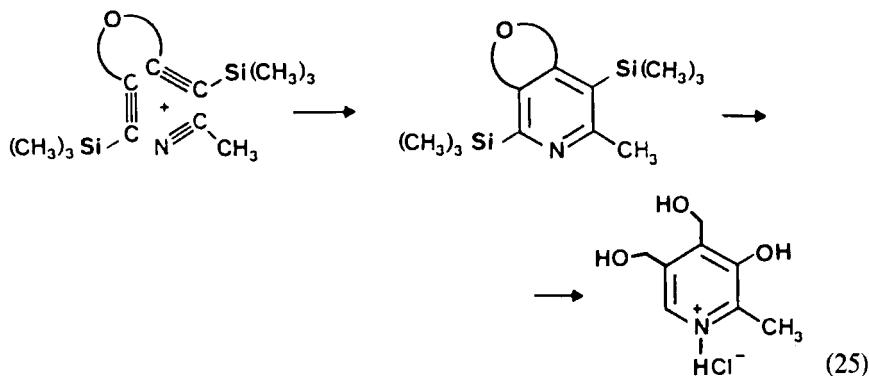
An interesting variation is the reaction of a diacetylene on $\text{cpCo}(\text{diene})$ systems [Eq.(24)]. 1,7-Octadiyne initially undergoes an intramolecular process to give a nonisolable intermediate containing a cyclohexane ring.



In the presence of excess nitrile, a second ring closure takes place at the cobalt and leads to derivatives of tetrahydroisoquinoline (21) in ~60% yield. Compound (22) is obtained analogously from 1,6-heptadiyne.

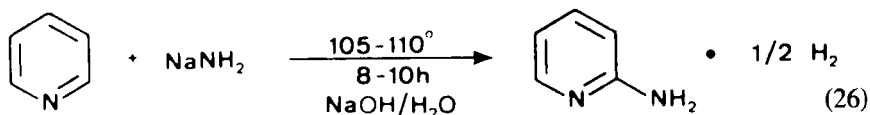


The annulated pyridines (21) and (22) are also obtained with $\text{cpCo}(\text{CO})_2$ as catalyst [77AG758, 77AG(E)708]. Using this variant of the cobalt-catalyzed cycloaddition, Schleich *et al.* opened up a new route to pyridoxine (Vitamin B₆) as its hydrochloride [Eq.(25)] (84HCA1274).

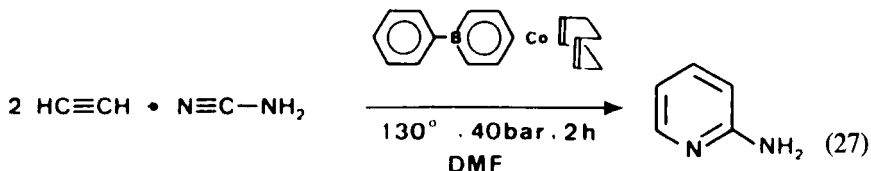


I. 2-AMINO- AND 2-ALKYLTHIO-PYRIDINES

2-Aminopyridines possess preparative interest and are conventionally prepared by substitution at ready-made pyridine rings. Pyridine may be converted into 2-aminopyridine using the so-called Chichibabin reaction in which pyridine is reacted with sodium amide in dimethylaniline [Eq.(26)].



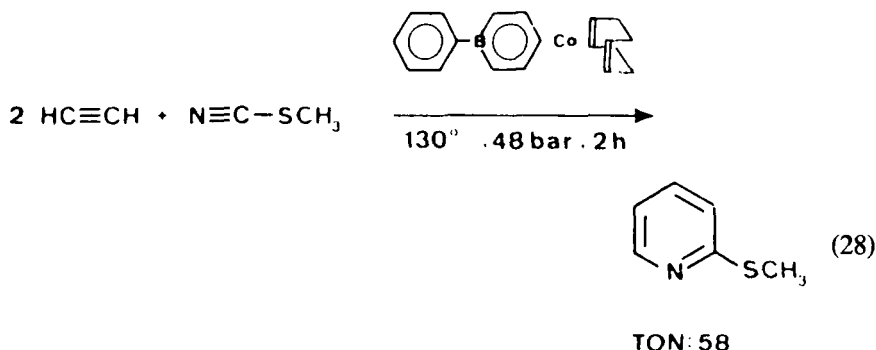
The product is obtained in 85% yield by treatment with aqueous NaOH followed by distillation (36GEP663891). 2-Aminopyridine is used in the manufacture of several chemotherapeutics, dyes for acrylic fibers, and as an additive for lubricants (71MI1). Monomeric cyanamide reacts with acetylene in the presence of the η^6 -borinato cobalt catalyst to give 2-aminopyridine [Eq.(27)]. For experimental details see Bönnemann and Brijoux (84MI7).



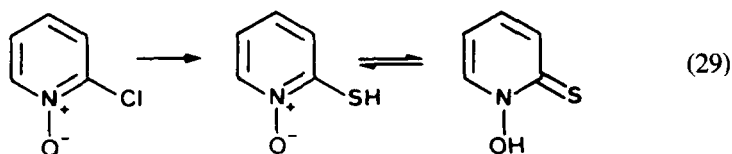
TON: 245

PROD: 0.39

Alkyl thiocyanates can also be used as the cyano component for the cobalt-catalyzed cycloaddition (80MI1) [Eq.(28)] (experimental details in 84MI8).



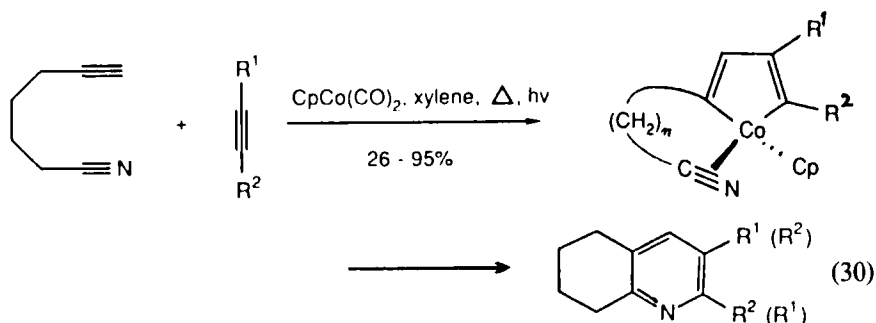
In this example the TON was not optimized. However, the catalytic reaction [Eq.(28)] seems to offer an easy entry into the pyridthione systems. The classical access to this is given in Eq.(29).



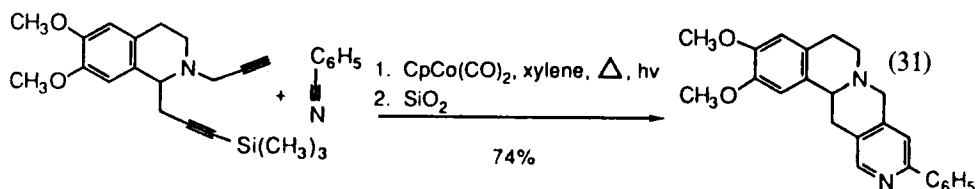
2-Chloropyridine-*N*-oxide reacts with sodium hydrogen sulphide to give pyridthione which, in the form of its zinc salt, is added to hair cosmetics as a general antifungal agent (50JA4362; 56USP2745826).

J. MISCELLANEOUS

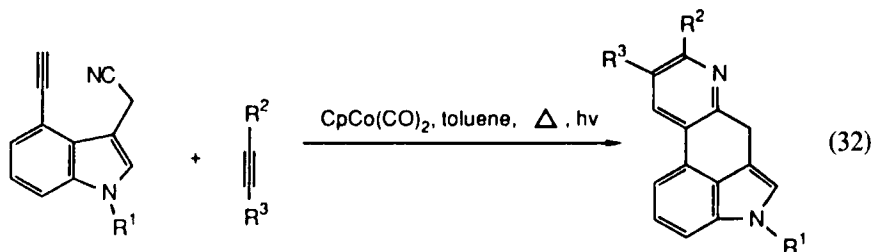
Based on the versatility of the pyridine formation, Vollhardt (74JA4996; 84AG525; 85T5791; 87MI3, 87MI4) has extensively varied the basic reaction of Eq.(1), using more sophisticated alkyne and nitrile precursors and $\text{cpCo}(\text{CO})_2$. This opened up the door to a number of polyheterocyclic systems having physiological interest. Bifunctional α -cyano- ω -ynes yield annelated pyridines [Eq.(30)] via a cobaltacyclic intermediate [77AG758; 77AG(E)708; 82CC133; 87MI5].



Using the general reaction of Eq.(30) a synthetic route to the isoquinino-[2,1-5]-2,6-naphthyridine nucleus was developed (83T905) [Eq.(31)].



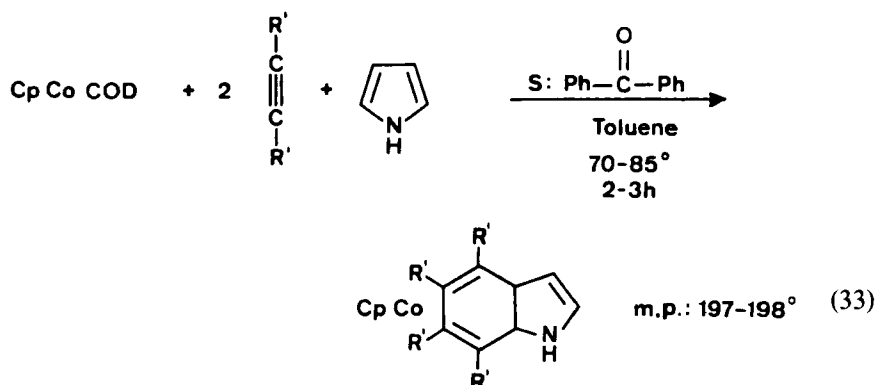
6-Heptynenitrile was incorporated into the indole system giving a pyridine derivative related to the ergot alkaloids (87MI4) [Eq.(32)].



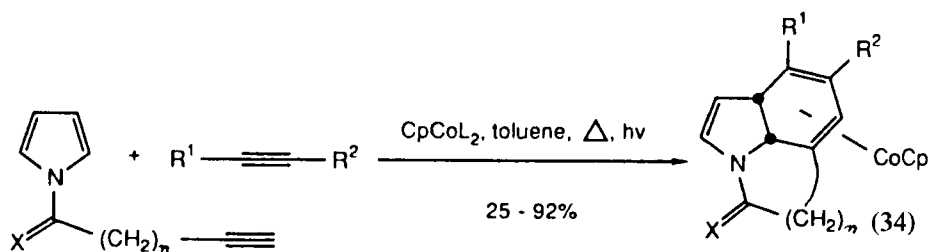
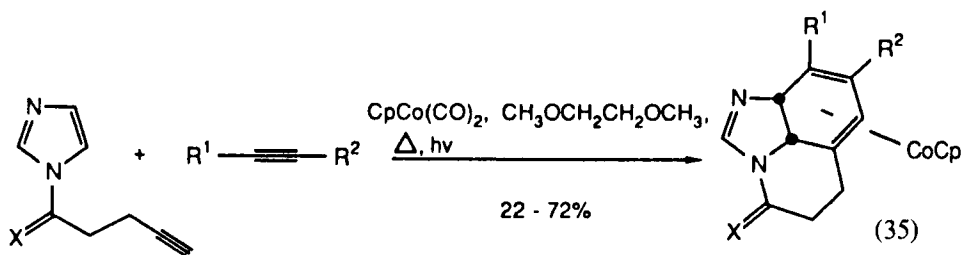
K. RELATED REACTIONS

The cobalt catalyzed cocyclization of alkynes with heterofunctional substrates is not limited to nitriles. cpCo -core complexes are capable of co-oligomerizing alkynes with a number of C,C, C,N or C,O double bonds in a Diels–Alder-type reaction. Chen, in our laboratories, has observed that these cycloadditions are best performed with the help of “stabilizers” such as ketones or acetic esters that are weakly coordinated to the cobalt and prevent the alkynes from being cyclotrimerized at the metal center

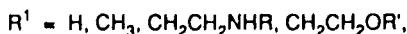
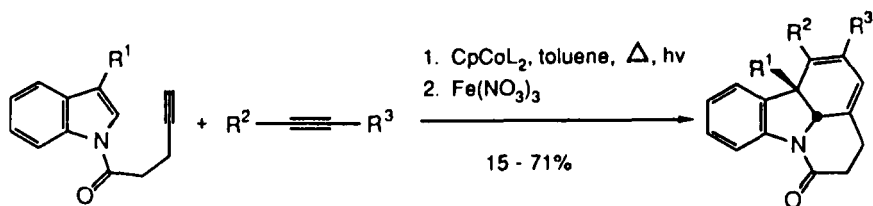
(87MI6). This modified cycloaddition may be used for the formation of dihydro-indole systems at cpCo [Eq.(33), where R = COOCH₃].



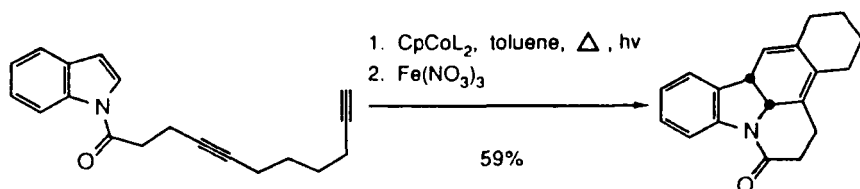
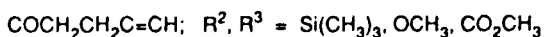
Similar cycloadditions of C,C bonds to the cobaltacycle have been brought about starting from substituted pyrrole and imidazole derivatives (86JOC5496; 87AG1067) [Eqs.(34) and (35)].


$$R^1, R^2 = \text{Si}(\text{CH}_3)_3, \text{CH}_2\text{CH}_3, \text{CO}_2\text{CH}_3, \text{OCH}_3;$$
$$X = \text{O}, \text{H}_2, \quad n = 2, 3$$

$$R^1, R^2 = \text{Si}(\text{CH}_3)_3, \text{CH}_2\text{CH}_3, \text{CO}_2\text{CH}_3, \text{OCH}_3;$$
$$X = \text{O}, \text{H}_2$$

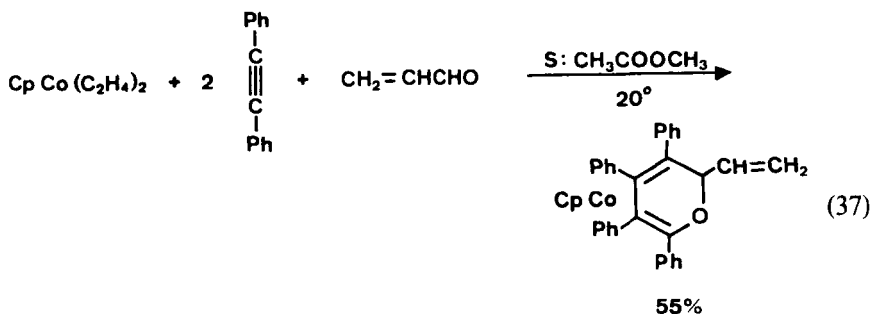
The resulting heterocycles can be structurally manipulated, e.g., reduced or desilylated either during complexation or after demetallation. Another possibility consists in using the primary products, obtained by the cobalt-mediated cycloaddition, as synthetic intermediates for further catalytic transformations. Indole derivatives have been cocyclized at cpCo to give 4a,9a-dihydro-9*H*-carbazoles or, after oxidation, precursors for strychnine (63T247; 86JA2091; 87MI7) [Eq.(36)].



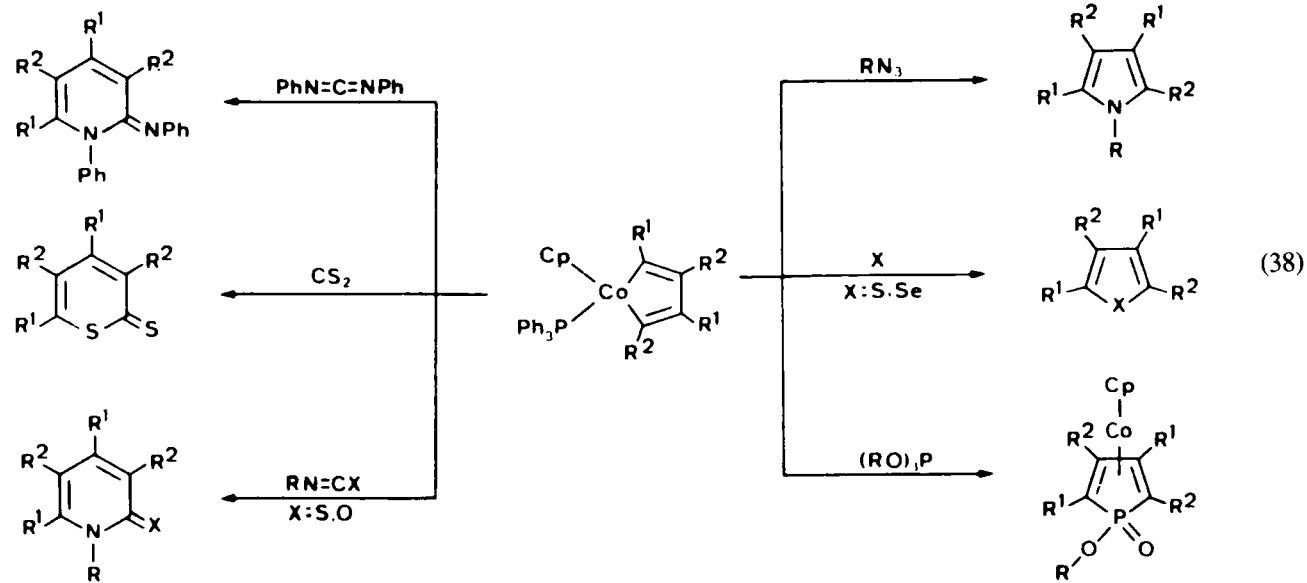
(36)



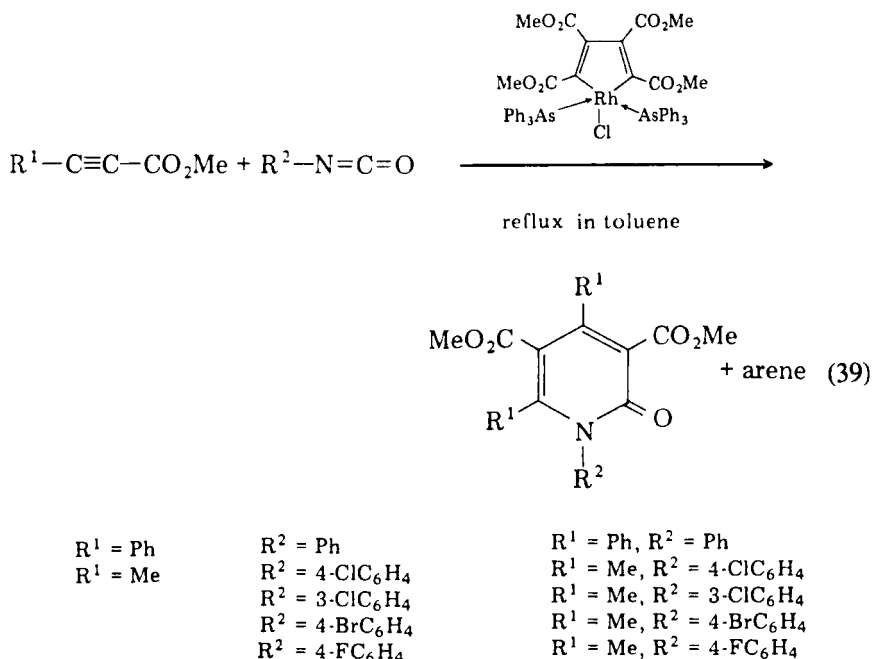
Remarkably, the cycloaddition of acrolein at the intermediate cobaltacycle selectively occurs at the carbonyl-, rather than at the C,C double bond, to give a vinylpyrane. In this cycloaddition, methyl acetate stabilizes the cpCo complex (87MI6) [Eq.(37)].



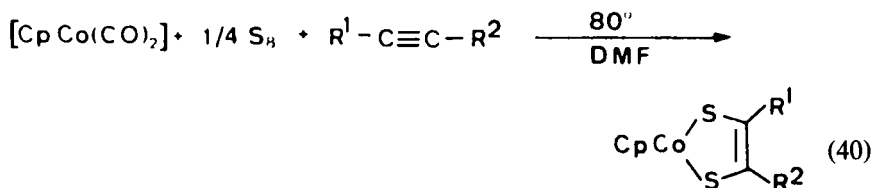
Further cycloadditions at the cobaltacyclopentadiene ring that lead to heterocycles have been comprehensively reviewed by Yamazaki (81MI1; 87MI8) [Eq.(38)],



and, among others, 6- and 5-membered heterocycles containing N, S, Se, and P have been prepared. The cocyclization of substituted alkynes and isocyanates to form 2-pyridones also occurs as the catalyst in the presence of a rhodium metallocycle (85MI1) [Eq.(39)].



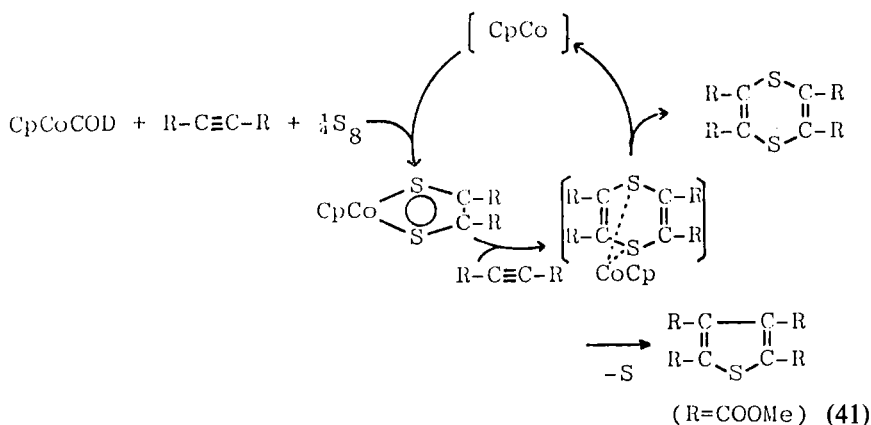
The insensitivity of the cpCo core even allows elemental sulfur to be incorporated in the alkyne cocyclizations, and a series of cpCo-dithiolatoethene complexes have been obtained using a simple one-pot procedure (82UP1; 83MI1) [Eq.(40)] (Table VII).



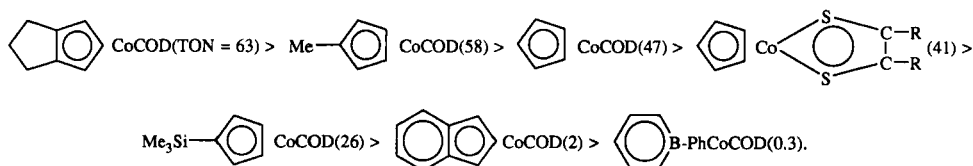
Kajitani has expanded this work to rhodium complexes [85JOM(293)C15] and included Se as the heteroatom (87CL245). In the presence of excess alkynes the cpCo core catalyzes the formation of thiophenes (83MI2; 84MI9) [Eq.(41)].

TABLE VII
cpCo-DITHIOLATOETHENE COMPLEXES ACCORDING TO Eq. (40)

Compound	Yield	Compound	Yield
$R^1 = H, R^2 = C_2H_5$	(15%)	$R^1 = R^2 = H$	(13%)
C_4H_9	(10%)	C_2H_5	(13%)
C_6H_{13}	(9%)	C_4H_9	(9%)
C_6H_5	(10%)	C_6H_5	(9%)
O		$COOCH_3$	(73%)
$C-CH_3$	(37%)	$COOC_2H_5$	(71%)
$COOH$	(20%)		
$COOCH_3$	(22%)		
$COOC_2H_5$	(44%)		
$(CH_2)_4C=CH$	(13%)		



This reaction can also be catalyzed by rhodium [85JOM(293)C15]. Systematic studies have revealed that the catalytic thiophene formation is sensitive to the controlling system Y at the cobalt (83MI2) (Scheme 5).



SCHEME 5

A comparison of the TON in Scheme 5 shows that the catalytic activities of the YCo(cod) complexes in the thiophene formation increase with increasing electron-donating ability of the ligand Y. The borininato-cobalt core shows the least activity, which is in contrast to the results found in the pyridine synthesis.

IV. Experimental Techniques

The batchwise synthesis of pyridines from nitriles and acetylene makes use of acetylene pressures of up to 6.9 MPa. The safety precautions mentioned in the "Technical Rules Acetylene" [62DOK(142)637; 80MI2] must be adhered to since acetylene (and propyne) can spontaneously decompose even in the absence of air or oxygen. The technical know-how for handling high pressure acetylene has been described by Bönnemann and Brijoux (84MI10). The pyridine synthesis is best performed in pure nitrile solutions that contain ~30–45% (weight) of acetylene. Optimized experimental procedures are reported by Bönnemann and Brijoux (84MI11).

In order to improve the catalytic TON, chemo-, and regioselectivity (in the case of monosubstituted alkynes), the reaction parameters have been systematically optimized for a large number of [YCoL] catalysts. This screening was performed in a continuous-flow reactor connected to a process chromatography set up (84MI12) (Fig. 1).

Solution of the educts and catalyst are pumped through the system, which is controlled by electronic balances. The actual reaction is performed in 87 ml continuous-flow reactor, from which samples are taken automatically and analyzed by gas chromatography (GC). The analytical data are processed online.

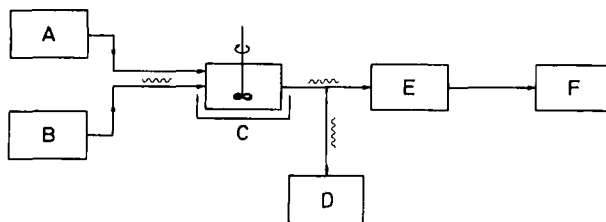
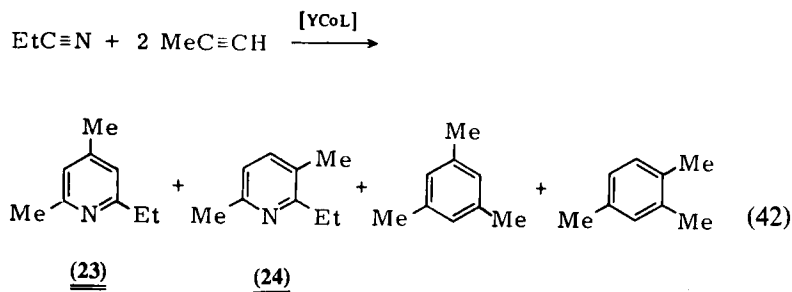


FIG. 1. Continuous-flow-apparatus for the optimization of homogeneous catalytic processes. A, catalyst solution; B, starting compounds; C, thermostated reactor; D, trap; E, gas-chromatograph; F, data evaluation.

V. Mechanistic Aspects

A. CONTROLLING FUNCTION OF LIGANDS Y AND L

As can be deduced from Eq.(2), the liberation of the catalytically active [YCo] species is of prime importance, the neutral ligand L merely stabilizing the catalyst as the isolable complexes YCoL. The influence of the neutral ligand at cobalt on the temperature at which initial pyridine formation occurred was investigated using the test reaction [Eq.(42)].



In this study, standard concentration ratios were adopted in the continuous-flow reactor [85AG(E)254] (Fig. 1). The temperature of the reactor was slowly increased and the conversion vs. temperature plot was monitored in the presence of various [cpCoL] complexes acting as catalysts (Fig. 2).

The activity of the individual [cpCo] compounds at low temperature is clearly dependent on the complexing ability of the neutral ligands (Fig. 2): the ethylene complex liberates the propagating [cpCo] species at room temperature, whereas the hexamethylbenzene complex shows activity first at 50–60°C (curve c), and the η^4 -cpH and cyclooctadiene (cod) complexes first cause propyne conversion at 75–85°C and 120–125°C, respectively (curve b and d). Above 120°C, the activity of the complexes is virtually identical; the neutral ligands have been almost completely displaced, so that the propyne conversion is now independent of the neutral ligand and is only controlled by the ligand Y at the cobalt. The chelating cod ligand is a good compromise between the weakly stabilizing ethylene and strongly complexed ligands such as CO. The carbonyl groups can, however, be displaced photolytically from the cobalt (84MI13).

The Y ligand remains attached to Co during the catalytical cycle. Thus, changing the Y ligand has a major effect on the generation and activity of the cobalt catalyst in the pyridine synthesis (Fig. 3). Whereas varying L does not affect catalyst activity at 150°C (Fig. 2), quite different activity at

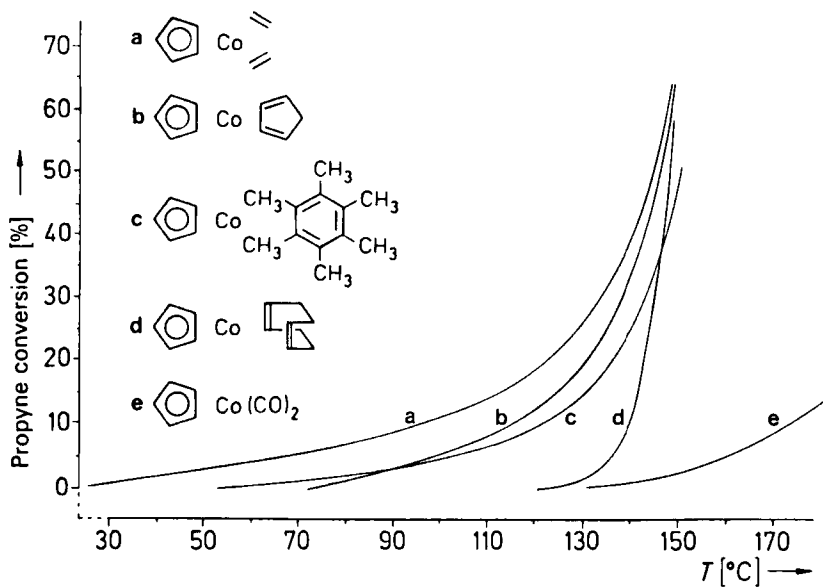


FIG. 2. Propyne conversion and reaction temperature for various $[\eta^5\text{-cpCoL}]$ complexes as catalysts.

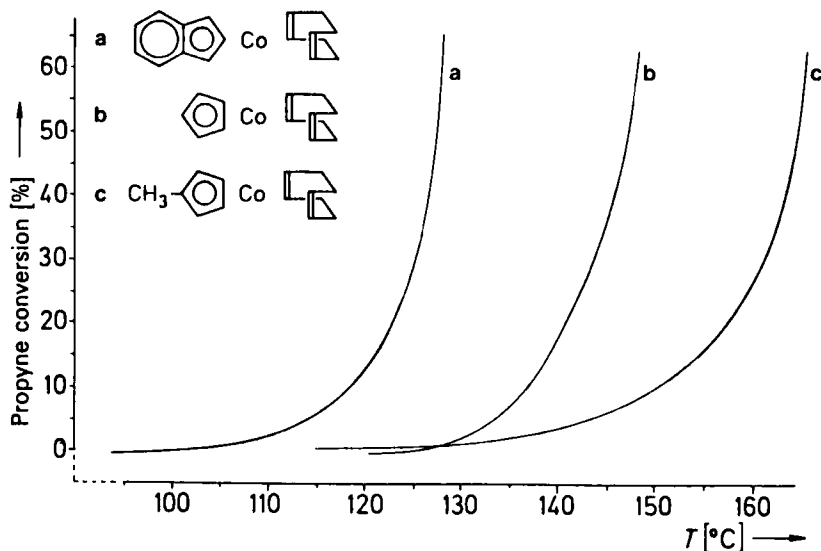


FIG. 3. Propyne conversion and reaction temperature for various $[\text{YCo}(\text{cod})]$ complexes as catalysts.

high temperature is observed as Y is varied. η^5 -IndenylCo(cod) shows initial activity at a temperature 25°C lower than that of the η^5 -cp-homolog; thus, Y may also have an influence on the dissociation of L. The selectivity of the cobalt catalyst is also affected by Y (see section VI.).

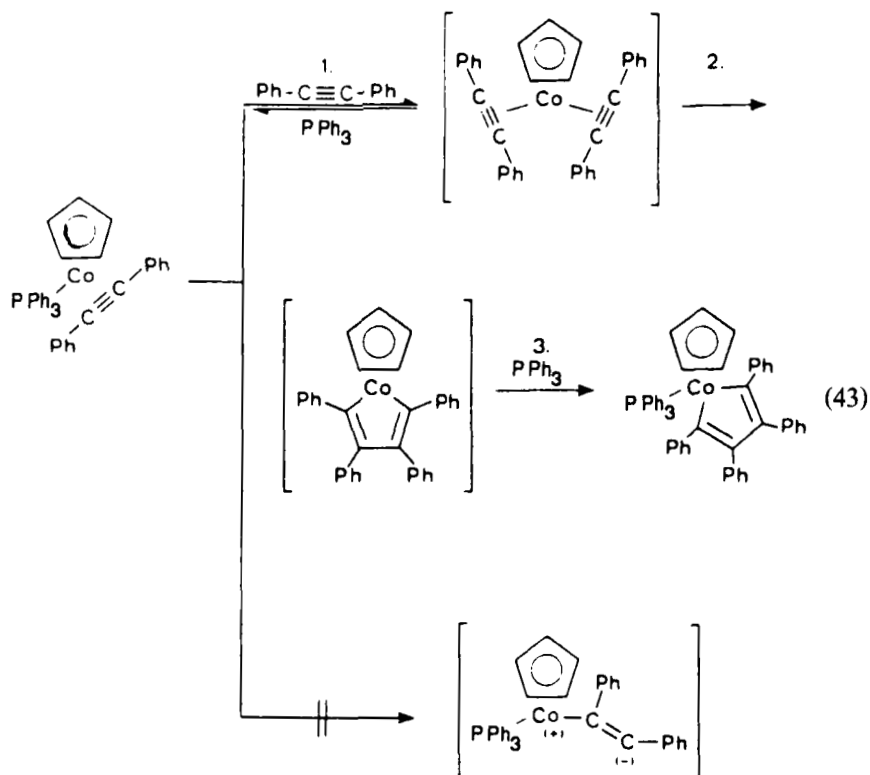
Methylcyclopentadiene (mecp) clearly illustrates the roles of Y and L. CpCo(η^4 -mecpH) has the same activity at 150°C as other cpCoL complexes, however, (η^5 -mecp)Co(cod) has lower activity than (cp)Co(cod) for a given temperature (Fig. 3) and shows different selectivity (85TH2). Hence, in order to optimize the activity and selectivity of the catalyst, an appropriate choice of the ligand Y must be made.

B. CATALYTIC CYCLE

As shown in Scheme 1, the initial step in the cobalt-catalyzed pyridine synthesis is the displacement of the neutral ligand L from [YCoL] complexes by the alkyne or nitrile. This can be brought about either by dissociation of L or by association of the substrates to the central metal. Bergman *et al.* studied the substitution of triphenylphosphine in η^5 -cpCo(PPh₃)₂ by Pme₃ and found a dissociative route involving a 16-electron [η^5 -cpCoPPh₃] intermediate (81JA1516). In related cases, Basolo *et al.* have noted that CO substitutions by phosphines in η^5 -cpRh(CO)₂ or η^5 -me₅cpRh(CO)₂, and η^5 -me₅cpCo(CO)₂, and phosphites proceed exclusively by associative pathways. To avoid a 20-electron configuration at the Rh or Co, they postulate a haptotropic shift ($\eta^5 - \eta^3$) of the cp ligand (66JA1657; 83MI3). However, Jonas *et al.* have prepared the stable, paramagnetic, 20-electron η^5 -cpCo η^6 -C₆Me₆ complex [85AG(E)295], and the associative route cannot be excluded. The displacement of the cod ligand in [YCo(cod)] complexes by norbornadiene in acetonitrile and benzene solutions was studied by Wakatsuki *et al.* (87MI9). The substitution reaction can be conveniently monitored by time dependent ¹³C-NMR spectroscopy and is found to be dependent on the solvent and the Y ligand, suggesting that both associative and dissociative pathways can occur. The solvent acetonitrile or an electron-withdrawing substituent at the cp accelerate the associative route, whereas, benzene as the solvent favors the dissociative pathway. In the case of Scheme 1, an associative pathway for the catalyst formation should be favored because a high nitrile concentration is present.

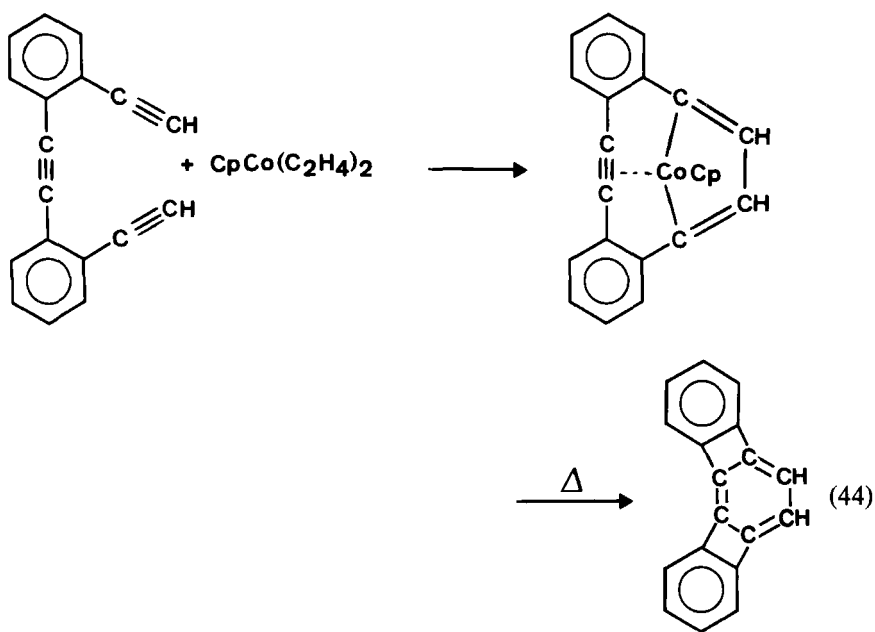
Yamazaki and Wakatsuki [77JOM(139)157] have contributed quite considerably to our understanding of the course of the cobalt-catalyzed pyridine synthesis by isolating a number of phosphine-stabilized cpCo complexes that may be regarded as plausible intermediates in the following

catalytic cycle: (1) stepwise addition of two alkyne molecules to the central metal atom, (2) ring closure to give a cobaltacyclopentadiene moiety, (3) insertion of the C,N triple-bond, followed by (4) elimination of the product [78AG517, 78AG(E)505]. The reaction of the triphenylphosphine-stabilized cpCo core with diphenylacetylene is an elegant model for this sequence [Eq.(43)].



Displacement of the phosphine from the metal occurs prior to coupling of the alkyne molecules (step 1) in a manner similar to the dissociation of L in Scheme 1. A consequence of this equilibrium is that the addition of excess phosphine (or other donor ligands) [78AG517, 78AG(E)505] reduces the rate of reaction. This observation, together with the fact that polar solvents have no influence on the rate, suggest that a polar intermediate is not involved, and the key step is the formation of a cobaltacyclopentadiene intermediate (step 2). This can be isolated as a stable phosphine-complex (step 3) that furthermore reacts with the nitrile to give the expected pyridine derivative [78JCS(D)1278]. Vollhardt (87MI4) first synthe-

sized an alkyne-stabilized cobaltacyclopentadiene moiety that was converted to the carbocycle upon heating [Eq.(44)].

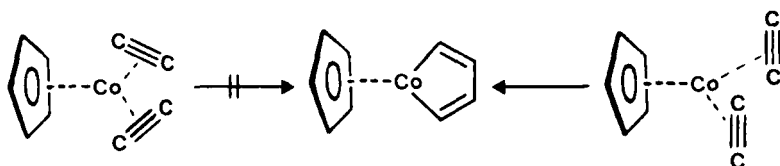


We have determined the rate of formation of dimethylethylpyridine, and trimethylbenzene in a batch reactor in the presence of $\text{cpCo}(\text{cod})$, which acts as the catalyst precursor. The reaction was found to be of order 1.7 with respect to alkyne and of zero order in nitrile concentration. The Arrhenius energy of activation for the formation of both pyridine and benzene derivatives was calculated to 22.8 kcal/mol (80MI3).

These results can be summarized as follows (1) the cobalt-mediated pyridine formation and alkyne cyclotrimerization depend on the square of the alkyne concentration and are independent of the nitrile concentration; (2) a common cobaltacyclopentadiene intermediate is responsible for both the pyridine and the benzene formation and may be regarded as a key intermediate for both hetero- and carbocyclic pathways.

According to Vollhardt (82CC953), the $\text{cp-cobaltacyclopentadiene}$ intermediate has a greater affinity for nitriles than for alkynes, and as a result, the reaction proceeds preferentially to give pyridine rather than benzene.

Wakatsuki *et al.* (83JA1907) studied the transformation of $\text{cpCo}(\text{bisalkyne})$ into $\text{cp-cobaltacyclopentadiene}$ by *ab initio* self-consistent field-molecular orbital (SCF-MO) calculations. For the $\text{cpCo}(\text{bisalkyne})$, they



SCHEME 6

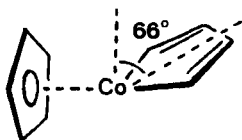
consider two conformations in which the alkynes are either coplanar or perpendicular to the cp-ring. They found that the cyclization of the perpendicular coordination is thermally forbidden in a least-motion process (C_{2v} symmetry), whereas that from a parallel conformation is allowed (C_s symmetry) (Scheme 6). The most stable conformation of the cp-cobaltacyclopentadiene was also calculated. In contrast to the expected geometry in which the cp ring is perpendicular to the cobaltacyclopentadiene, a conformation having an angle of 66° was found to have the lowest energy (Scheme 7). The energy difference was calculated to be ~ 4 kcal/mol. The transformation of cpCo(bisalkyne) to cp-cobaltacyclopentadiene is an endothermic reaction with a calculated energy of 14 kcal/mol.

The nitrile triple bond can react in two ways with the mononuclear cobaltacycle:

(1) A Diels–Alder type of addition (Fig. 4a) can occur through a cobaltanorbornadiene intermediate, followed by reductive elimination, to yield the product and regenerate the cp-Co core (77JA1666).

(2) Complexation of the nitrile to the cobalt atom (end-on or side-on) can occur followed by insertion into the cobalt–carbon bond to give a seven-membered intermediate (Fig. 4b).

Yamazaki and Wakatsuki originally favored the Diels–Alder addition (Fig. 4a) [77JOM(139)169] (without, however, presenting any experimental evidence) but later, [78JCS(D)1278] they adopted the pathway involving the 7-membered cobaltacycle (Fig. 4b). Bergman and co-workers (77JA1666) have obtained kinetic evidence indicating that both pathways are possible (for the mechanistically related cyclotrimerization of al-



SCHEME 7

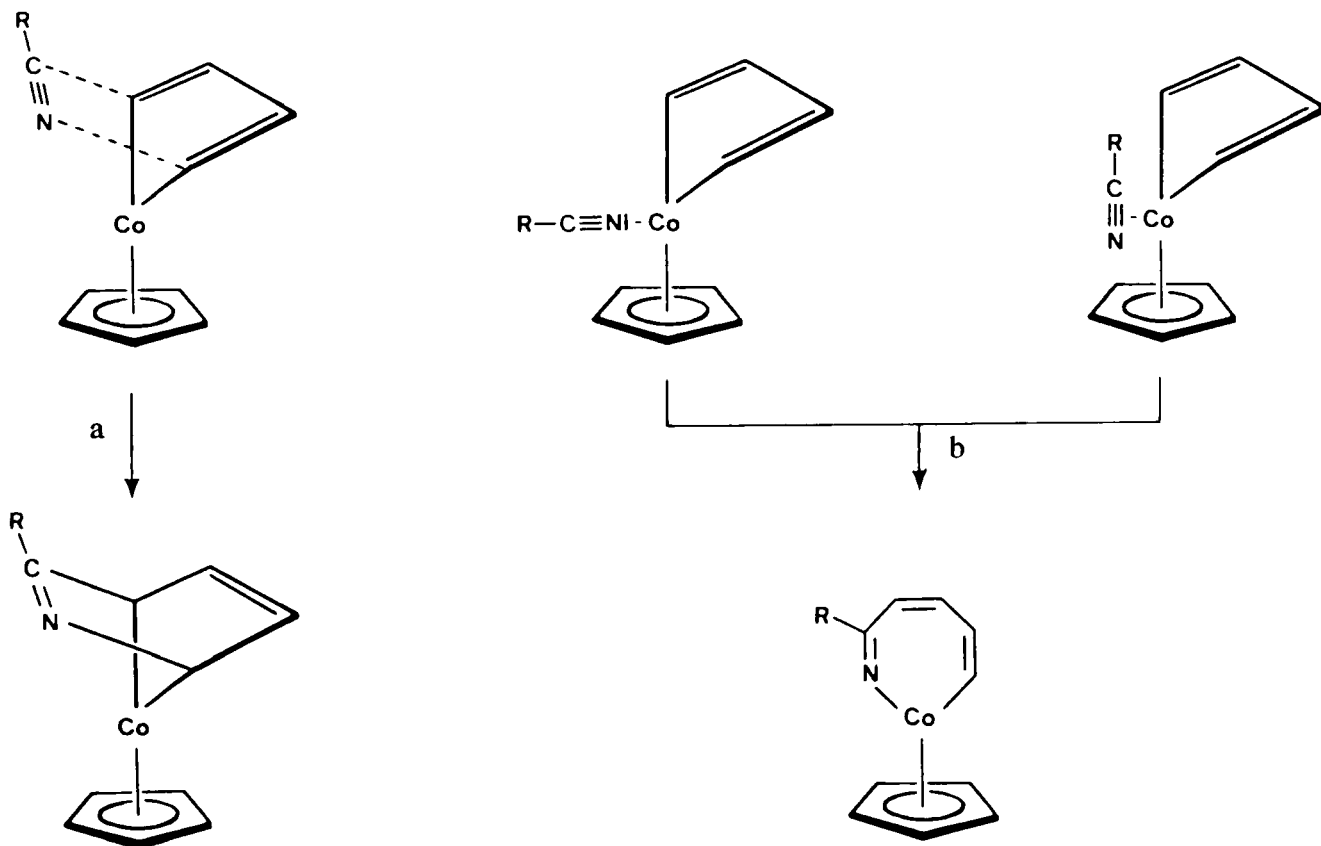
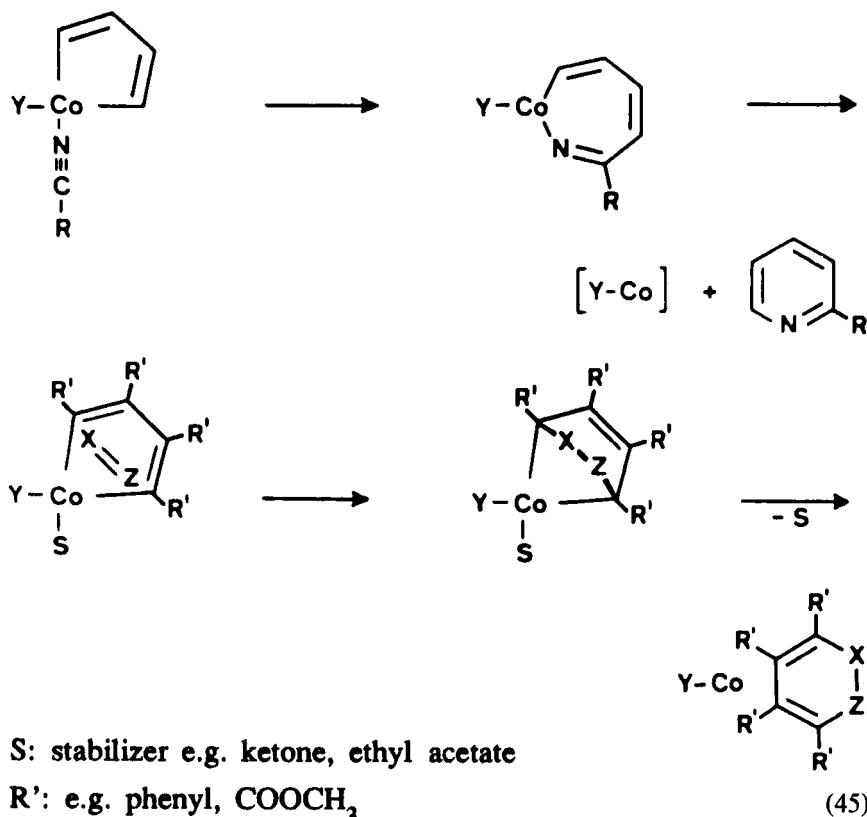
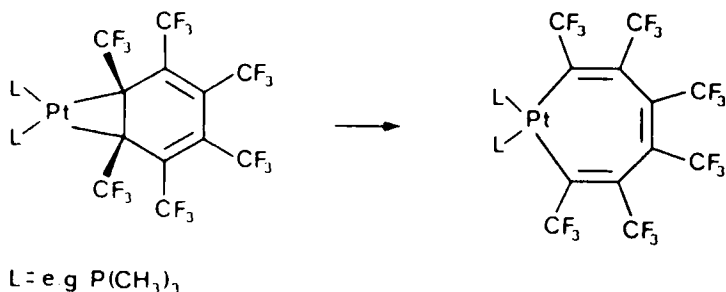


FIG. 4. The reaction of a nitrile with the cobaltacyclopentadiene intermediate: a, Diels-Alder addition; b, insertion into the Co—C bond.

kynes), however, the Diels–Alder reaction seems to occur only with alkynes having strongly dienophilic character. Since alkylcyanides are known to be poor dienophiles, the pathway shown as (Fig. 4a) appears to be unlikely. The observation that the thermal Diels–Alder addition of acrylonitrile to, for example, butadiene occurs almost exclusively to the C,C double bond to give a cyclohexene derivative also points to a different mechanism (Fig. 4), whereas in the cobalt-catalyzed formation of 2-vinylpyridine via cobaltacyclopentadiene, reaction occurs exclusively through the C,N triple-bond.

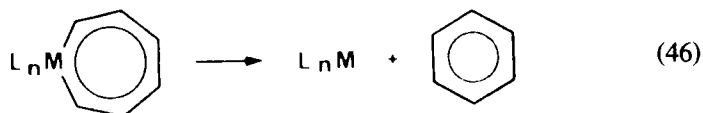
In some cases, it is possible to promote the Diels–Alder-type reaction. We have found that in the presence of polar auxiliary ligands (stabilizer), the Co-mediated reaction of alkynes with activated C,C or C,O double bonds takes place (87MI6). These findings are only understandable if there is a direct interaction between the cp-cobaltacyclopentadiene and the polar stabilizer, which may act by blocking free coordination sites at the Co [Eq.(45)].





SCHEME 8

Analysis of the products formed by reacting monosubstituted alkynes with nitriles [Eq.(42)] suggest that in the postulated seven-membered intermediate (Fig. 4b), bonding to the Co atom occurs exclusively through the nitrogen atom. Hoffmann and Stockis have carried out calculations suggesting that in such metallocycles, heteroatoms more electro-negative than carbon will preferentially adopt sites α to the metal (80JA2952). Although no direct evidence is available as to the mechanism of the final reductive elimination step that leads to product formation, it has been suggested [79NJC(3)39] that "mononuclear metallacycloheptatrienes are not likely to be very stable, since cis-reductive elimination of benzene from d^6 -complexes can be a symmetry allowed and (probably) thermodynamically favorable reaction" [Eq.(46)].



Interestingly, the reversal of this reaction has also been observed (75CC723): reaction of a substituted benzene coordinated to platinum is accompanied by ring opening (Scheme 8).

Finally, it should be mentioned that rearrangement of the cp-cobaltacyclopentadiene intermediate to the thermodynamically more stable $[(\eta^5\text{-cp})\text{Co}(\eta^4\text{-cyclobutadiene})]$ complex (which is catalytically inactive) is a thermally forbidden process [Eq.(47)].



VI. Relations between Catalyst Structure and Effectivity

A comparison of a series of $[\text{YCo}(\text{cod})]$ catalysts in the test reaction (Scheme 5) under identical conditions in the continuous-flow apparatus (Fig. 1) has revealed that the reaction temperature required for 65% propyne conversion depends on the nature of the controlling ligand Y. Further, an inspection of Table VIII reveals that both the Arrhenius energy of activation E_A for the reaction and the selectivity of the catalyst are strongly controlled by the ligand Y [85AG264, 85AG(E)248].

The me_3cpCo system shows the lowest activity in the test reaction [Eq.(42)], whereas the benzoylcyclopentadienyl system, which is 1000 times more reactive, shows the highest activity among the substituted cpCo catalysts. Mesomeric substituent effects influence the activity more than inductive effects, so that replacement of a methyl- by a chloro-substituent only has minor influence on the activity. The regioselectivity is in general inversely proportional to the catalyst activity. Exceptions are found when $\text{Y} = 1,2-(\text{Me}_3\text{Si})_2\text{cp}$ and Ph_4cp . In these cases, both high regioselectivity and activity are found. This is probably due to the accumulation of sterically demanding substituents.

TABLE VIII
 ^{59}Co -NMR SHIFT OF $[\text{YCo}(\text{COD})]$ CATALYST IN DEPENDENCE OF Y^a

Y = $\eta^5\text{-cp}$ derivatives	E_A^b (Kcal/mol)	T(°C) ^c	$\Delta T(^\circ\text{C})$	Regioselectivity		$\delta(^{59}\text{Co})$	δ_{rel}
				(23)	(24)		
$(\text{CH}_3)_5\text{C}_5$	26.8	220	+73	77.8	22.2	-1413	-237
Biscyclo[3.3.0]octadienyl	24.6	180	+33	71.4	28.6	-1261	-85
$\text{CH}_3\text{---C}_5\text{H}_4$	23.6	162	+15	66.9	33.1	-1227	-51
$\text{Cl---C}_5\text{H}_4$	24.0	170	+23	64.2	35.8	-1199	-23
C_5H_5	22.8	147	0	63.1	36.9	-1176	0
$t\text{-Bu---C}_5\text{H}_4$	23.0	152	+5	63.9	36.1	-1166	+10
$\text{Me}_3\text{Si---C}_5\text{H}_4$	22.6	144	-3	62.5	37.5	-1149	+17
$\text{C}_6\text{H}_5\text{---C}_5\text{H}_4$	22.4	140	-7	63.4	36.6	-1088	+88
$\text{CH}_3\text{CO---C}_5\text{H}_4$	21.5	123	-24	59.3	40.7	-1055	+121
$\text{C}_2\text{H}_5\text{CO---C}_5\text{H}_4$	21.6	124	-23	58.7	41.3	-1051	+125
$\text{CH}_3\text{OCO---C}_5\text{H}_4$	21.6	125	-22	61.1	38.9	-1047	+129
$\text{OHC---C}_5\text{H}_4$	21.8	129	-18	58.8	41.2	-1033	+143
$\text{C}_6\text{H}_5\text{CO---C}_5\text{H}_4$	21.3	119	-28	55.0	45.0	-1001	+175

^a $\delta(^{59}\text{Co})$ of $\text{K}_3\text{Co}(\text{CN})_6 = 0$.

^b E_A , Arrhenius energy of activation.

^c T, Reaction temperature for 65% propyne conversion.

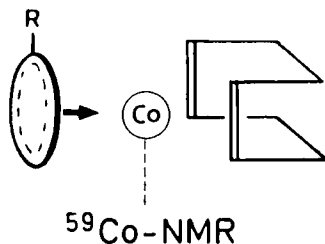


FIG. 5. Determination of ligand effect by $^{59}\text{Co-NMR}$ spectroscopy.

The electronic influence of Y on the central metal is easily determined from the $^{59}\text{Co-NMR}$ shift (Fig. 5), particularly by comparing the chemical shift of the substituted cobalt complexes relative to the parent complex: $\delta_{\text{rel}} [\text{RcpCo}(\text{cod})]$ against $\delta_{\text{rel}} [\text{cpCo}(\text{cod})] = 0$. Alkyl groups act to shield the cobalt nucleus, whereas phenyl or acetyl groups deshield the nucleus. These effects are additive: $\delta_{\text{rel}} = -237$ ppm for $(\text{me}_5\text{cp})\text{Co}(\text{cod})$ and is five times higher than $\delta_{\text{rel}} = -51$ ppm for $\text{cpCo}(\text{cod})$. Similar substituent effects on the activity and $^{59}\text{Co-NMR}$ chemical shift have been observed for the η^5 -indenyl based catalysts.

If one plots the $\delta_{\text{rel}} (^{59}\text{Co})$ values against the Arrhenius energies of activation determined for the $[\text{RcpCo}(\text{cod})]$ and $[(\text{R-indenyl})\text{Co}(\text{cod})]$ catalysts, then an almost linear correlation is found (Fig. 6). The linear relationship between the Arrhenius energy of activation and $\delta_{\text{rel}}(^{59}\text{Co})$ can also be expressed by the regressional Eq.(48),

$$E_A (\text{kcal/mol}) = 23.3 - 0.0133 \cdot \delta_{\text{rel}}(^{59}\text{Co}) \quad (48)$$

in which the significance level is 95% (Fisher test) and the correlation coefficient $r = 0.91$. Substituted cpCo systems that have $^{59}\text{Co-NMR}$ s shifted to a higher field are less active than $\text{cpCo}(\text{cod})$, whereas $(\text{Rcp})\text{Co}(\text{cod})$ complexes with large positive δ_{rel} values are particularly active. A similar quasilinear correlation has been established between regioselectivity and $^{59}\text{Co-NMR}$ shift in the cp- and indenyl-cobalt series [85AG(E)258]. The relationship between $^{59}\text{Co-NMR}$ shift and the activity of the cyclopentadienyl- and indenylcobalt catalysts suggests there may be a dependence of catalytic activity on the electron distribution at Co [84JOM(272)231].

The observed differences in the catalytic properties of the R-cpCo complexes might be explained by steric, electronic, or field effects of the substituent. It is generally accepted that the replacement of H by R alters

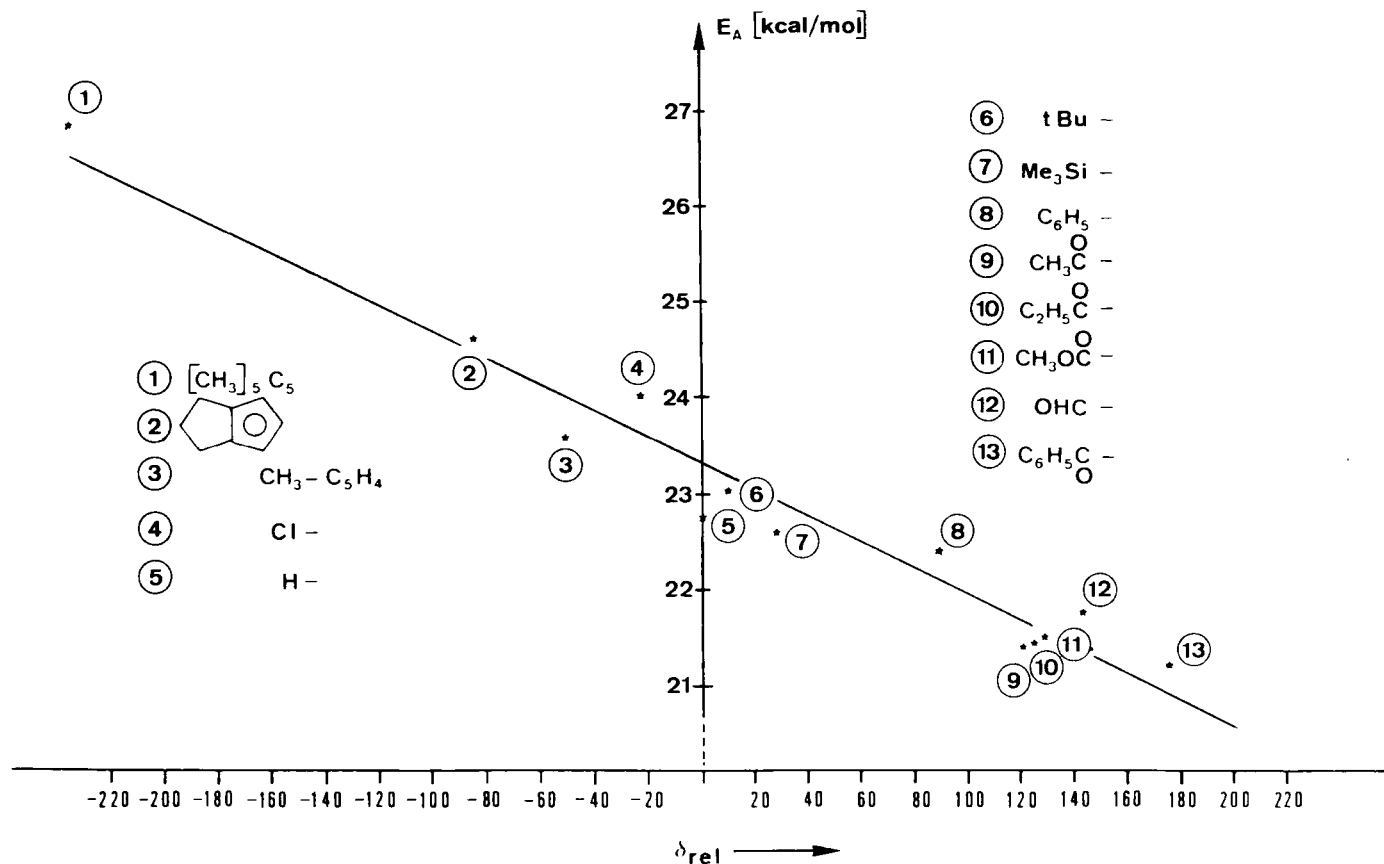


FIG. 6. Correlation between Arrhenius energies of activation (E_A) and ^{59}Co -NMR chemical shifts for Rcp Co (cod) catalysts.

the steric influence of the cp ring. An increase or decrease in electron density along the R-cpCo bond axis in dependence of the substituent R has also been discussed. Brill and co-workers (84MI1) have shown that me_3cp inductively donates more electron density than cp, but the increase at the Co is only small. Extended Hückel calculations by Arthurs *et al.* [85JOM(291)231] indicated that the charge on Rh in CHO-cpRh 2,4-dimethylpenta-1,4-diene is only 0.03 e higher than that in the unsubstituted complex (+0.21 e). Therefore, we can conclude that the substituent at the cp ring has little effect on the charge on the Co atom and is presumably not responsible for the observed large differences in the catalytic activity of the complexes. The steric effect of the Y ligand should also be negligible: biscyclo[3,3,0]octadienyl deactivates, whereas indenyl activates. Wakatsuki *et al.* (87MI9) tried to explain the effect of electron-withdrawing substituents through space interaction of the substituent dipole with the *d*-electrons of the Co atom; they found a good correlation between the field parameter of the organic substituent with the ^{13}C -NMR chemical shift of the coordinated olefinic carbons in the diene. However, this idea fails for halogen substituents, which, like alkyl groups, deactivate the R_5cpCo catalysts.

Krüger and Angermund (85UP2; 86TH1) have carried out high resolution X-ray structure analysis involving determination of electron deformation density on the complexes. A comparison of the crystal structures shows that substitution by an electron donating group at the cp ring results in an orthogonal orientation of the R—C bond with respect to the double bonds of the complexed cod. If R is an acceptor, the R—C bond is parallel to the cod double bond. This compares well to the findings of Chinn and Hall (83JA4930) in the structures of substituted cpCo- and cpRh-dicarbonyl complexes, that substituting an electron-withdrawing substituent on the cp ring forces the complexes into a staggered rather than an eclipsed form. In R-cpCo(cod) systems, Krüger and Angermund have found that even small changes in the electronic character of the R-cp ligand cause significant changes in the electron density distribution around the cobalt.

The structure-activity relationship for cobalt catalysts in the pyridine synthesis can be summarized in the following manner: If the substituent R is a donor, the ^{59}Co -NMR signals are shifted to higher field and the catalytic activity decreases. If R is an acceptor, the ^{59}Co -NMR signal is shifted to lower field and the activity increases. Donor substituents are oriented orthogonal to complexed cod in the catalyst precursors; acceptors are oriented parallel. The deformation of the spherical charge distribution about cobalt is also dependent on the nature of R.

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Chemistry of Pyrazoles Condensed to Heteroaromatic Five- and Six-Membered Rings

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I. Introduction

Although only a few condensed 5:6 or 5:5 aromatic pyrazole derivatives can be isolated from biological sources, the chemistry of condensed pyrazoles has received considerable interest. Condensed pyrazoles with an indene skeleton can be considered as purine analogues and, as such, are expected to have biological activity. The discovery of the xanthene oxidase inhibitory action of pyrazolo[3,4-*d*]pyrimidine and the cAMP phosphodiesterase inhibitory action of pyrazolo[1,5-*a*]pyrimidines has stimulated considerable interest in the synthesis of analogues of both ring systems.

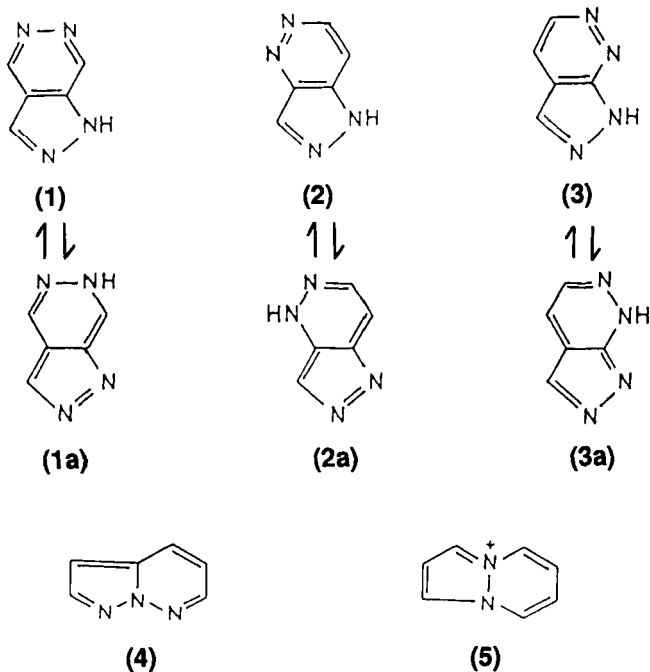
In previous work (85MI1; 87AHC319), the synthesis and chemistry of pyrazolopyridines and pyrazolopyrimidines was surveyed. This chapter reports synthetic approaches to other aromatic 10 π electron systems containing a pyrazole moiety, as well as the systems' main chemical and physicochemical properties.

II. Synthesis of Pyrazoloazines

A. SYNTHESIS OF PYRAZOLOPYRIDAZINES

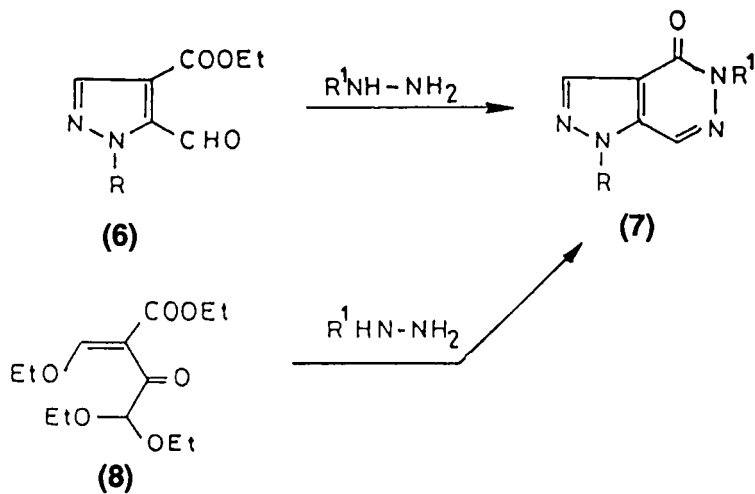
Four aromatic pyrazolopyridazines (**1–4**, 1*H*-pyrazolo[3,4-*d*]-pyridazine, 1*H*-pyrazolo[4,3-*c*]-pyridazine, 1*H*-pyrazolo[3,4-*c*]-pyridazine and pyrazolo[1,5-*b*]pyridazine, respectively) and one pyrazolopyri-

dazinium salt (pyrazolo[1,5-*b*]pyridazine, **5**) are possible. Systems **1–3** can display tautomerism (**1a–3a**, 6*H*-pyrazolo[3,4-*d*]pyridazine, 4-*H*-pyrazolo[4,3-*c*]pyridazine, and 7*H*-pyrazolo[3,4-*c*]pyridazine, respectively, as examples). Although none of the parent ring systems has yet been synthesized, derivatives of all ring systems are known.

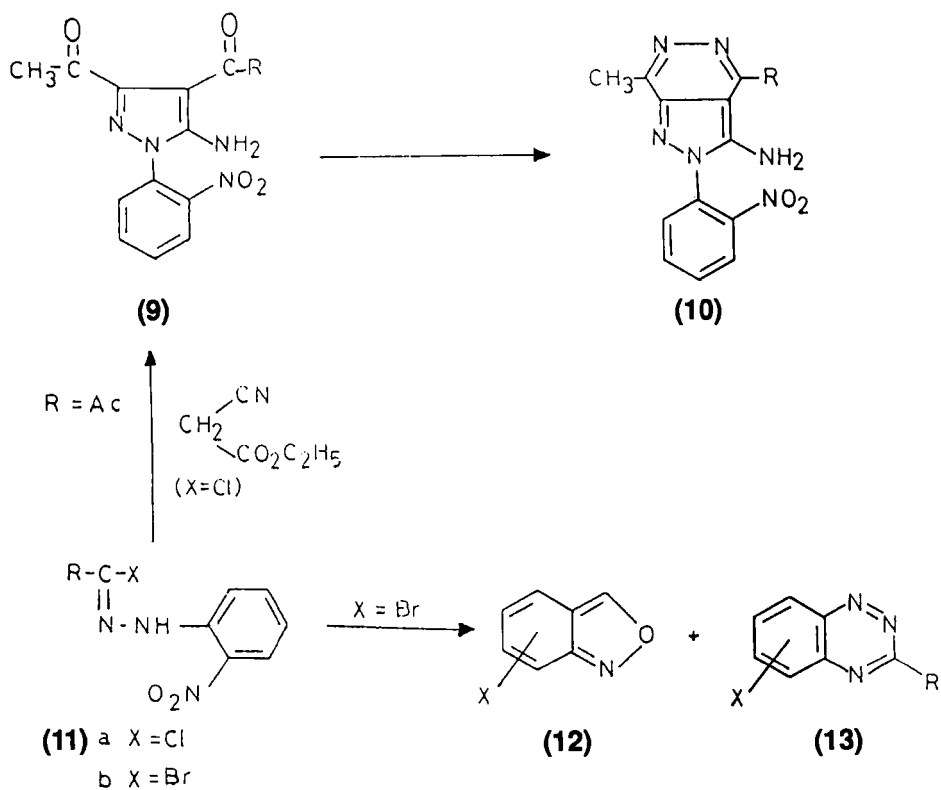


1. Pyrazolo[3,4-*d*]pyridazines (**1**)

Derivatives of this ring system (**1**) are prepared both from pyrazole intermediates (73T435; 75BSF1268, 75FRP223591; 77JHC75, 77JHC375, 77T45; 78JHC813; 81JAP71010] and from pyridazine intermediates (85CPB982). Thus, 4-ethoxycarbonylpyrazol-5-al (**6**) is converted into pyrazolo[3,4-*d*]pyridazines (**7**) upon treatment with hydrazine hydrate in refluxing ethanol. The same derivatives are obtained upon treatment of the oxoester **8** with hydrazines (Scheme 1). Several 5-oxopyrazole 4-carboxylic acid esters, pyrazole-4,5-dicarboxylates, and 5-oxo 4-cyanopyrazoles were converted into pyrazolo[3,4-*d*]pyridazines upon treatment with hydrazines (56JA159; 56MI1; 64G210; 69BSF2061; 71BSF1336; 74MI1; 75BSF2185; 77HCA2171; 84G261). Pyrazole-3,4-dials



SCHEME 1

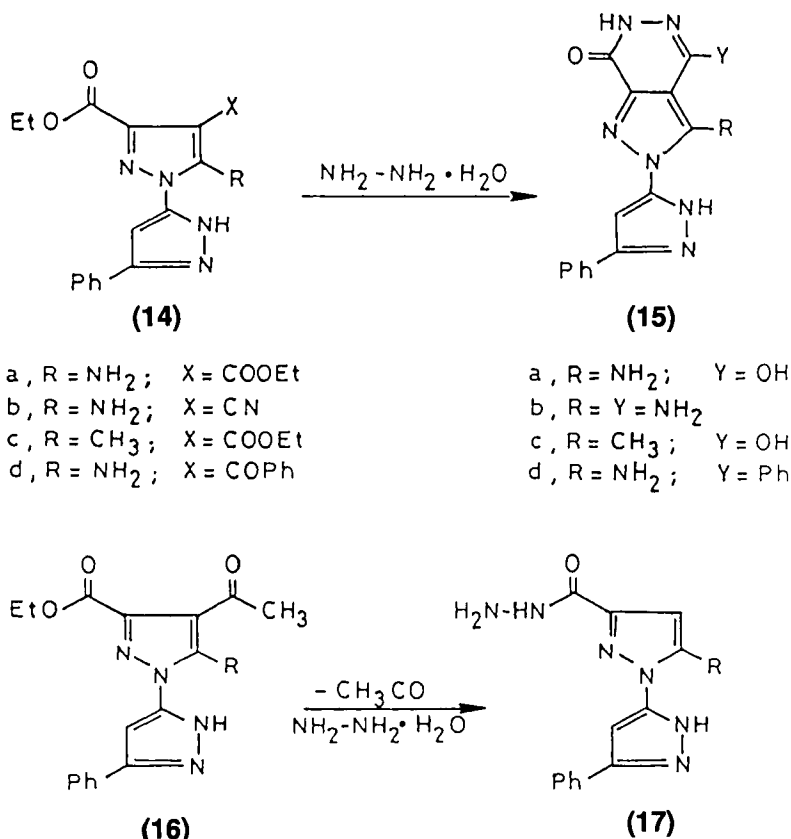


condense with hydrazines to afford pyrazolo[3,4-*d*]pyridazines (69BSF2061).

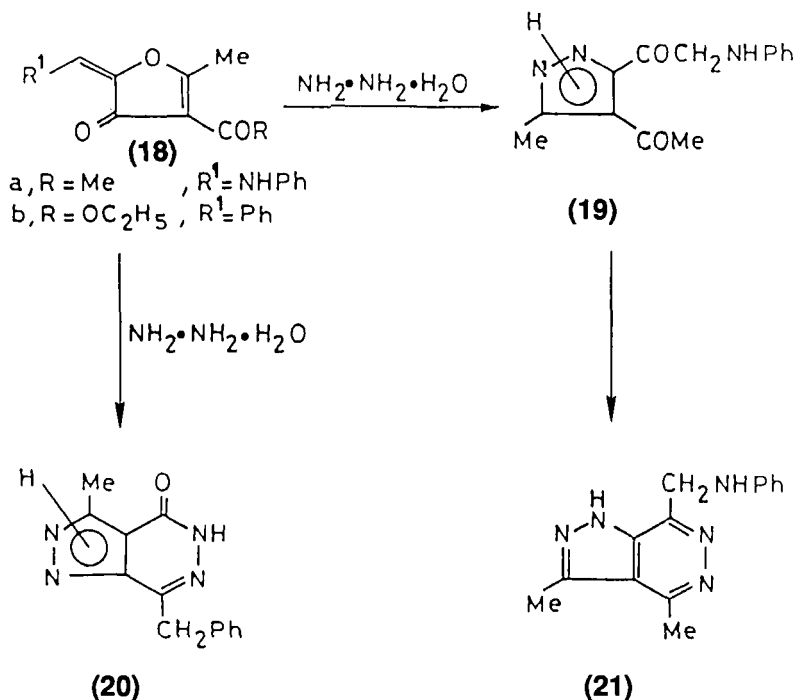
It was reported (82H319) that **9** reacts with hydrazines to yield **10**. Compounds **9** were prepared via reacting **11a** with ethyl cyanoacetate. This is in contrast to the reported formation of **12** and **13** upon attempted condensation of **10b** with ethyl cyanoacetate (83JHC511).

Treatment of pyrazoles **14a-d** with hydrazine hydrate affords pyrazolo[3,4-*d*]pyridazines **15a-d**. However, an attempt to convert **16** into a pyrazolo[3,4-*d*]pyridazine resulted in acyl group cleavage and the formation of **17** (Scheme 2) (77HCA2171).

Chantegral, Hartmann, and Gelin (77T45) reported synthesizing **21** from the reaction of **18a** with excess hydrazine. The intermediate pyrazole derivative **19** was isolated. The reaction of **18b** with hydrazine directly afforded **20** (Scheme 3).



SCHEME 2

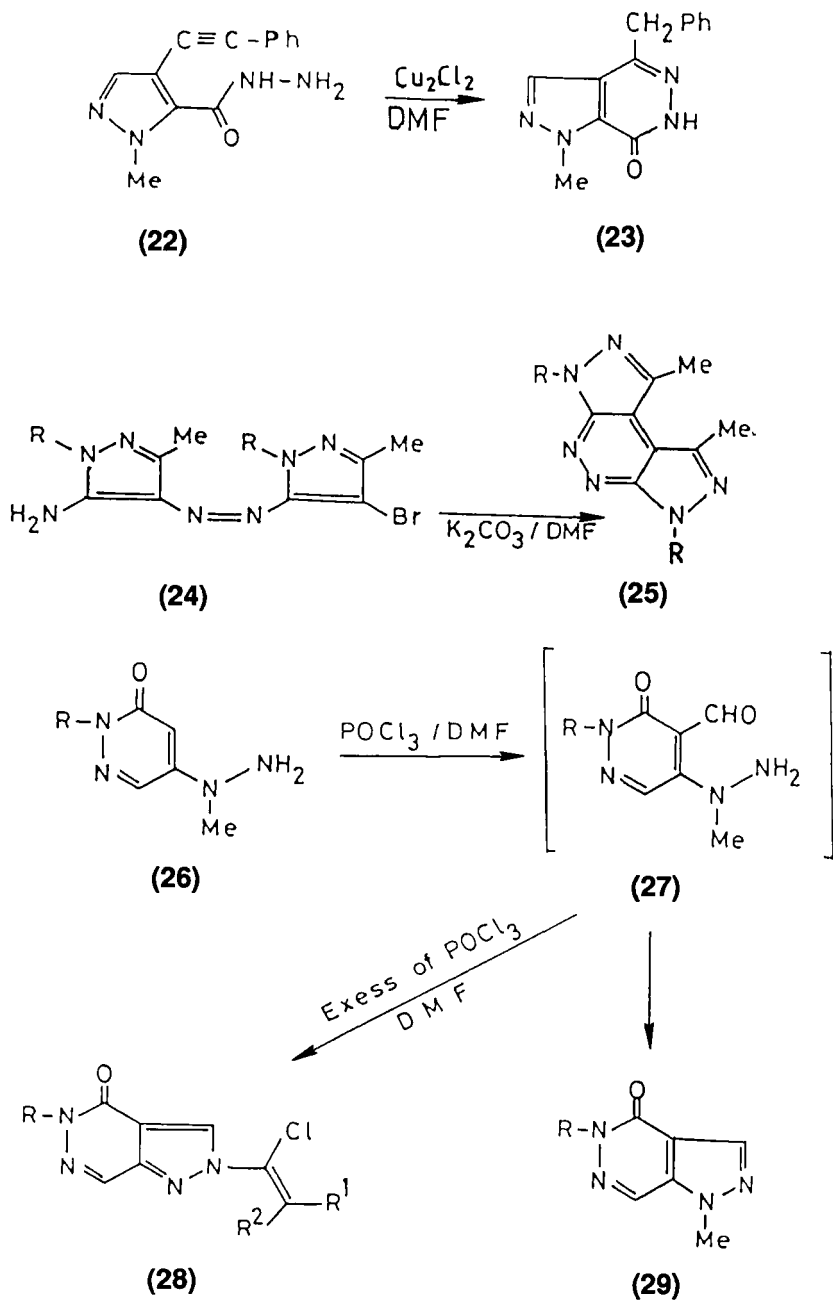


SCHEME 3

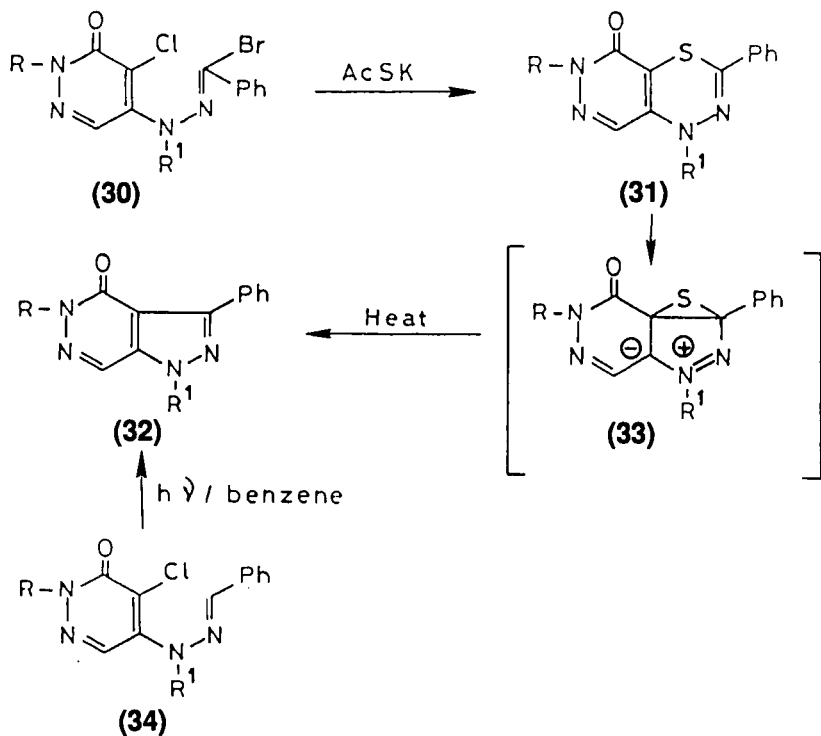
Treatment of hydrazide **22** with cuprous chloride in dimethylformamide (DMF) affords **23** (85IZV1367), whereas treatment of **24** with K_2CO_3 and $\text{Ni}(\text{NO}_3)_2$ at 130°C in DMF gives **25** (80KGS1524). The cyclization of hydrazinopyridazine (**26**) with phosphorus oxychloride in DMF afforded either **28** or **29** depending on reaction conditions; **27** is a common intermediate (Scheme 4) (85CPB982).

Treatment of **30** with potassium thioacetate afforded pyrazinothiazine (**31**) which, when heated or treated with alkali, afforded pyrazolo[3,4-d]pyridazinone **32**, most likely via intermediate **33**. Sulfur elimination from the latter gave **32**, (Scheme 5) (84CPB4437; 84H479). Compounds **32** are also obtained via irradiation of hydrazones **34** (75MI1; 84JHC1249; 85CPB982).

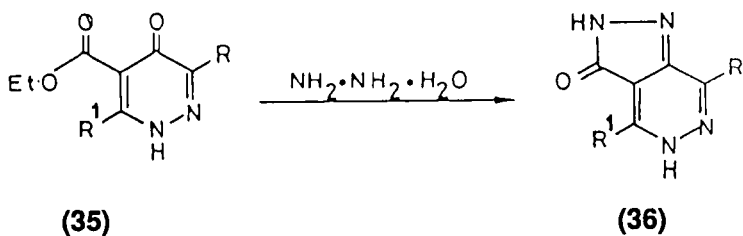
Ethyl 4-oxopyridazine-5-carboxylates (**35**) afford pyrazolo[3,4-d]pyridazine (**36**) upon treatment with hydrazine. Similarly, treatment of 4-cyanopyridazinone with POCl_3 followed by hydrazinolysis gave pyrazolo[3,4-d]pyridazines (84CB3349).



SCHEME 4



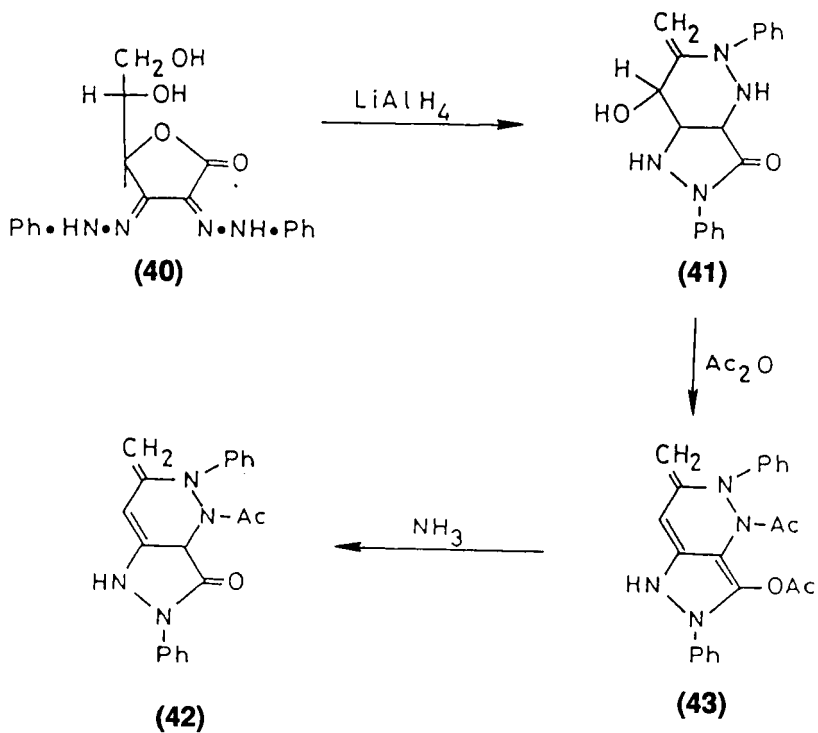
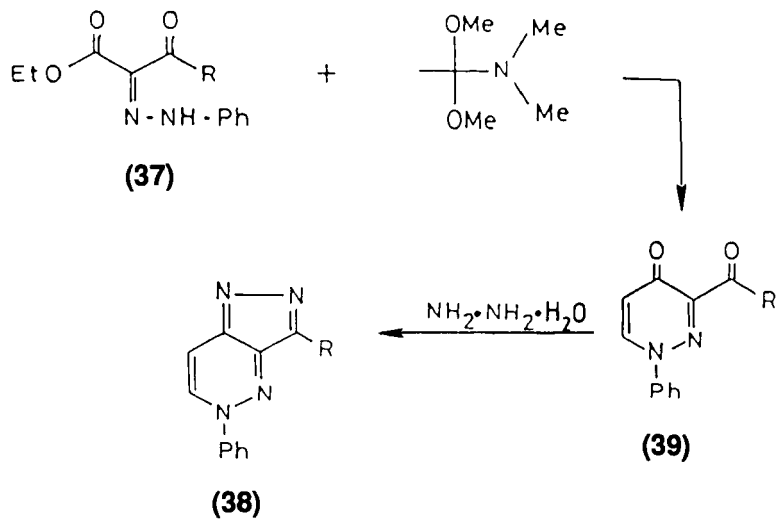
SCHEME 5

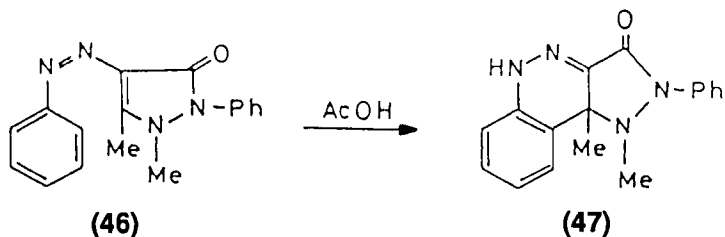
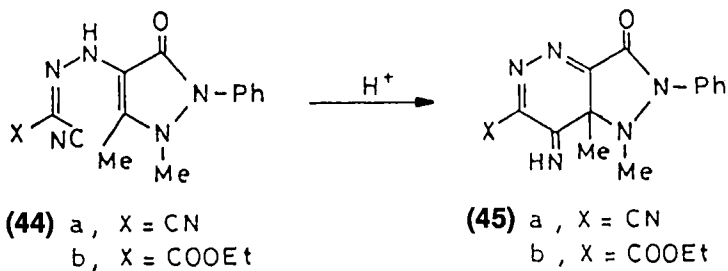


2. Pyrazolo[4,3-*c*]pyridazines (2)

Pyridazinone (39), prepared via reacting 37 with *N,N*-dimethylacetamide dimethyl acetal, afforded pyrazolo[4,3-*c*]pyridazine (38) upon treatment with hydrazine (Scheme 6) (81JHC333).

Reduction of dehydro-*c*-ascorbic acid phenylhydrazone (40) with LiAlH_4 resulted in hydrogenation of the hydrazone residue and cyclization to bicyclic compound 41, which was dehydrogenated with boiling acetic anhydride during acetylation to give diacetate 43, then partly hydrolyzed to monoacetate 42 (Scheme 7) (72JOC3523).

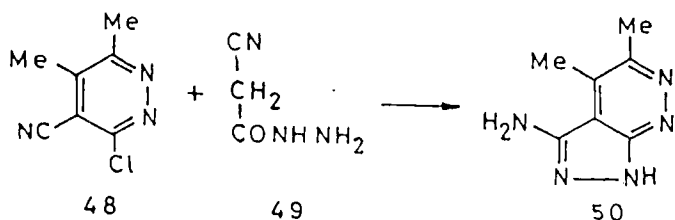


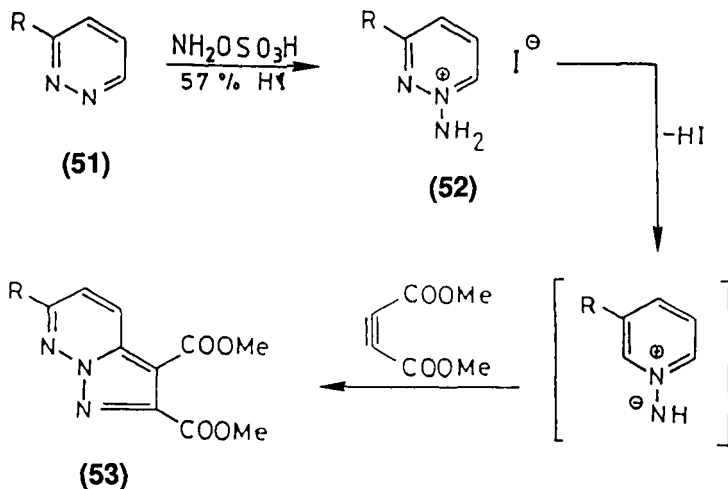


Hydrazones **44a,b** were cyclized to **45a,b** upon treatment with mineral acids [82JCS(P)989]. This is similar to the reported cyclization of **46** to **47** upon refluxing in acetic acid (78TH1).

3. *Pyrazolo[3,4-c]pyridazines (3)*

The only reported synthesis of **3** utilizes the reaction of 6-chloro-5-cyano-3,4-dimethylpyridazine (**48**) with cyanoacethydrazide (**49**) whereby **50** is formed (58AG513).





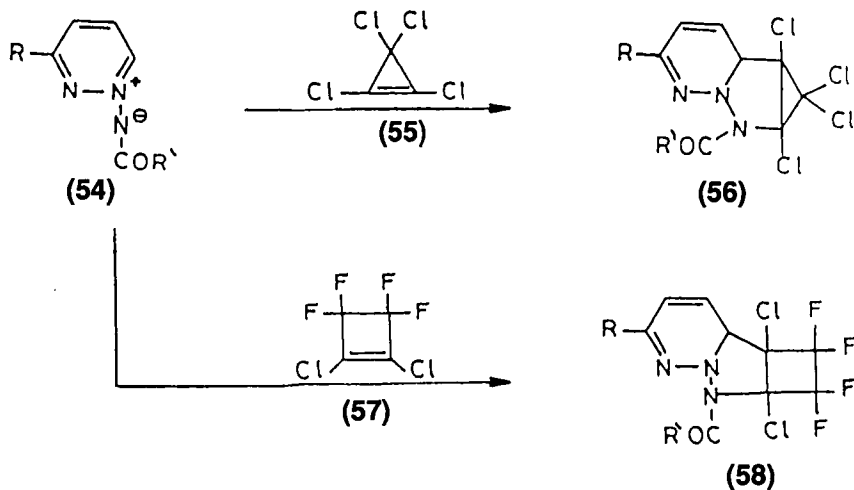
SCHEME 8

4. *Pyrazolo[1,5-*b*]pyridazines (4)*

Several derivatives of this ring system are synthesized from *N*-aminopyridazinium salts (74CC941, 74CPB1814; 79MI2; 81H753; 83JAP58134094). Thus, *N*-aminopyridazinium iodides (52), prepared via treatment of 51 with sulfonyl azides or hydroxylamine-*o*-sulfonic acid, react with dimethyl acetylenedicarboxylate to yield 53 (Scheme 8) (74CPB1814). Quite similar is the reaction of aminimide 54 with 55 to yield 56. The reaction of 57 with 54 affords 58 (Scheme 9) (79MI2; 81H753).

5. *Pyrazolo[1,2-*a*]pyridazines (5)*

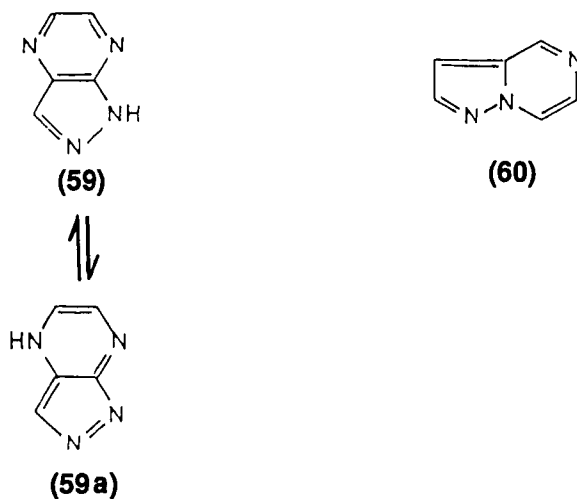
Reduced derivatives of this ring system are obtained either via addition of dienes to 1-pyrazolines or via alkylation of pyrazolidine or pyridazolidines with the suitable dihalogen compound [59AP225; 64MI1; 66AP441; 69JOC2720; 69LA150; 72JHC41; 74GEP2526358; 77JAP83687; 85JCS(P2)71]. Reportedly, perhydropyridazine-3,6-diones react with cinnamaldehyde to yield 1-phenyl-1*H*-pyrazolo[1,2-*a*]pyridazines. However, the authors cited did not present convincing evidence that excludes possible formation of acyclic aminimides (83MI3).



SCHEME 9

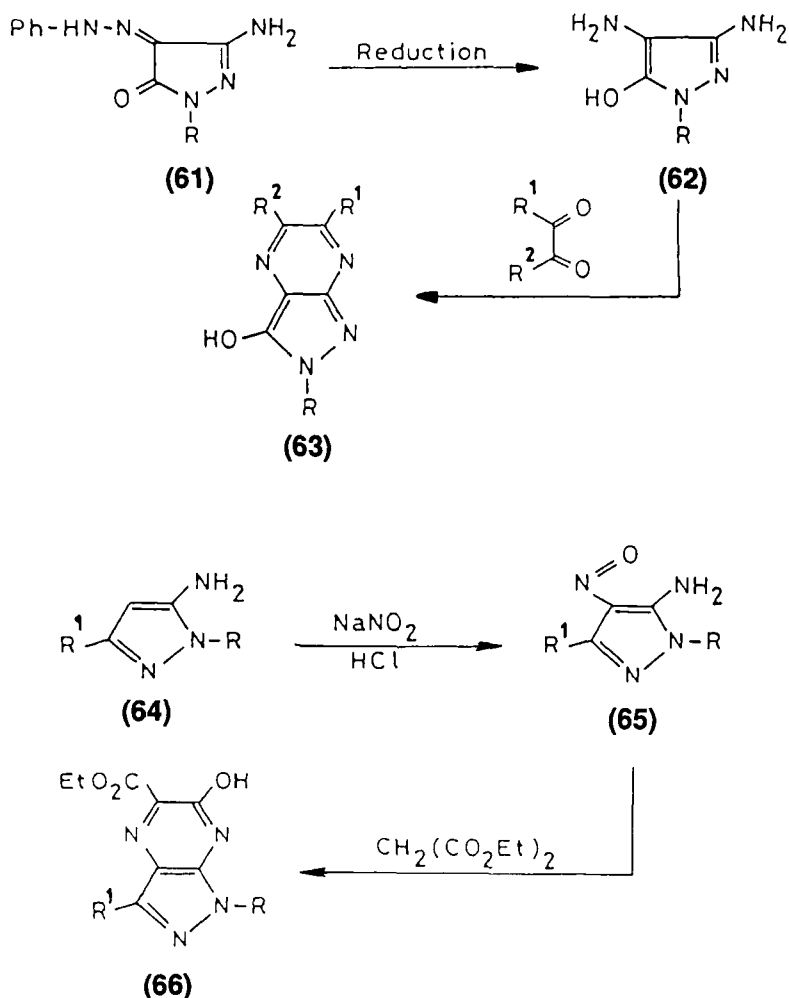
B. SYNTHESIS OF PYRAZOLOPYRAZINES

Only two isomeric pyrazolopyrazines are possible: 1*H*-pyrazolo [3,4-*b*]pyrazine (59) and pyrazolo[1,5-*a*]pyrazine (60). Derivatives of both ring systems are known. Annular tautomerism could occur in 59 [cf. 4*H*-pyrazolo[3,4-*b*]pyrazine (59a)].



1. *Pyrazolo[3,4-*b*]pyrazines (59)*

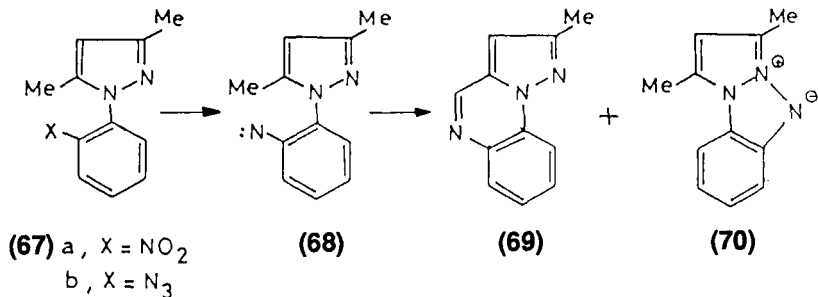
Derivatives of this ring system are obtained by condensing 3,4-diaminopyrazoles with 1,2-dioxo compounds [09JPR1; 36G649; 56JA5451; 58JA421, 58JA3752; 61AG15, 61MI1; 68JCS(C)2159; 82FES116; 83FES24]. Thus, condensation of **62** (prepared via reduction of **61**) afforded **63** upon treatment with 1,2-diones (58JA3752; 61AG15). Nitrosation of **64** afforded **65**, which condensed with diethyl malonate to yield pyrazolo[3,4-*b*]pyrazine (**66**) (Scheme 10) (73G1105; 76USP3957782).



SCHEME 10

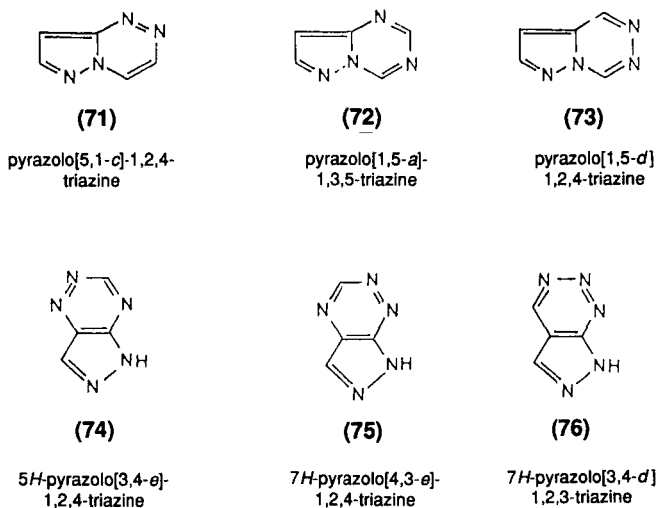
2. *Pyrazolo-1,5-a*pyrazines (60)

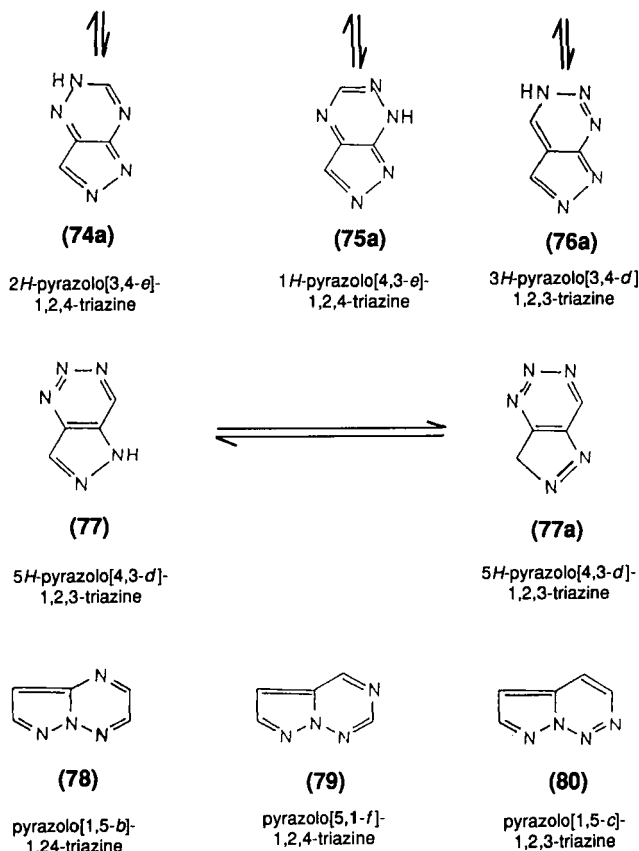
Nitrene **68**, derived by nitro group deoxygenation of **67a** or by thermolysis of azide **67b**, cyclized to a mixture of **69** and **70** [80JCS(P1)982].



C. SYNTHESIS OF PYRAZOTRIAZINES

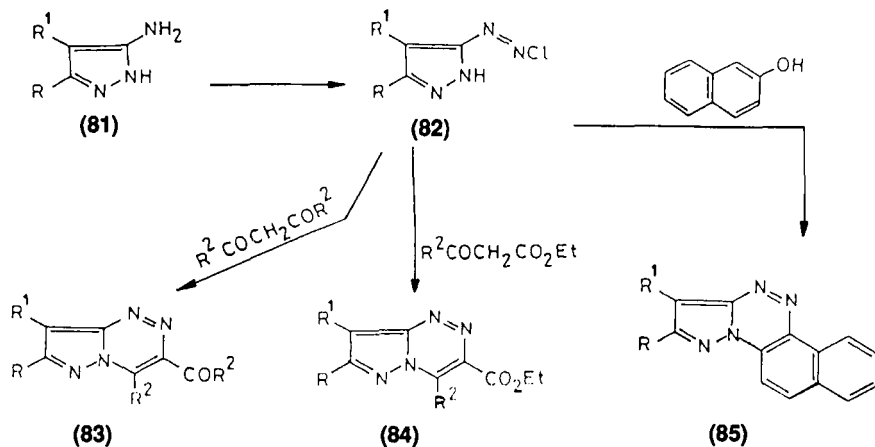
Ten isomeric pyrazolotriazines are theoretically possible (**71–80**). Derivatives of **71–76** have already been prepared. Neither parent **77** nor any of its tautomers has yet been made. Derivatives of **74–77** can display tautomerism (cf. **74a–77a**). Aromatic pyrazolo[1,2-*a*]-1,2,3-triazines can exist only as salts or dipolar molecules.





1. *Pyrazolo[5,1-c]-1,2,4-triazines (71)*

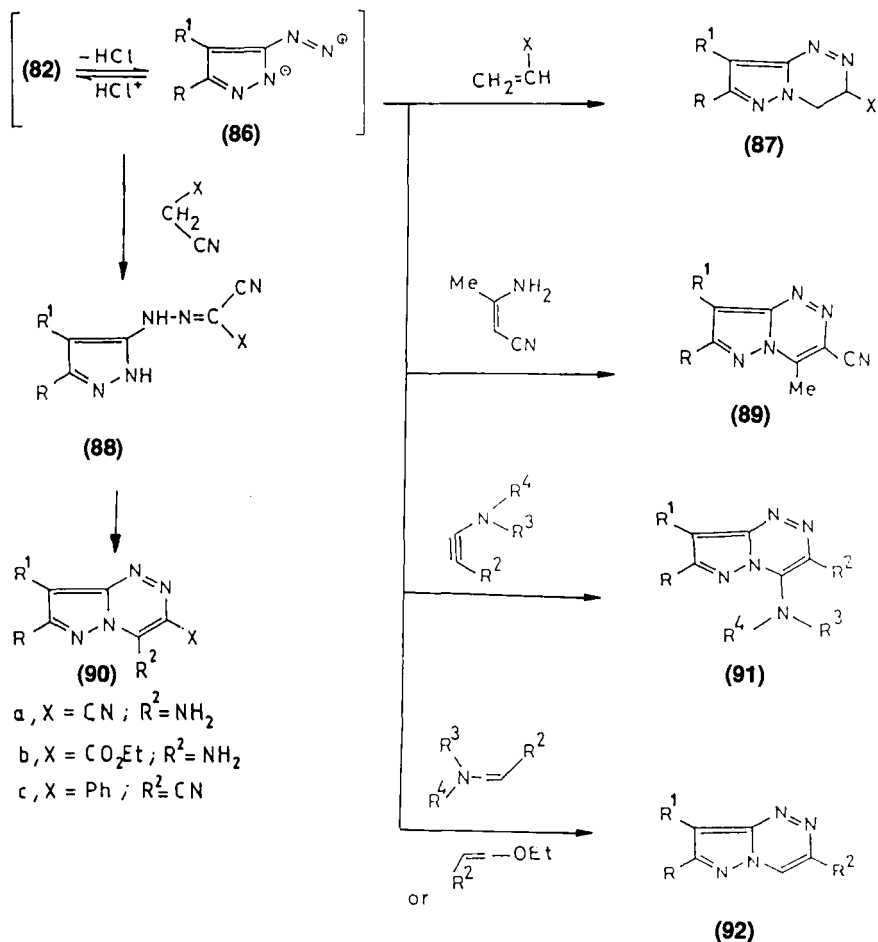
The synthesis of derivatives of **71** was described in connection with investigations on reactivity of diazopyrazoles in cycloaddition reactions [76JOC3781; 77JA633, 77JHC227, 77S556; 78JCS(P1)885, 78ZN(B)218; 81M245; 83AP713, 83JOC2330; 84MI1]. Reimlinger (66CB3350) reported the formation of pyrazolo[5,1-c]-1,2,4-triazine derivatives (**85**) upon attempted coupling of diazotized **81** with β -naphthol; a cyclocondensation reaction took place under the coupling reaction conditions (Scheme 11). Kocivar *et al.* (76T729) observed also that diazotized **81** affords cyclic triazines **83** upon coupling with β -diketones. Kocivar *et al.* (76T729) assumed the acid formed during coupling catalyzed the cyclization. El-nagdi *et al.* (82H559) reported that, coupling **82** with β -ketoesters afforded



SCHEME 11

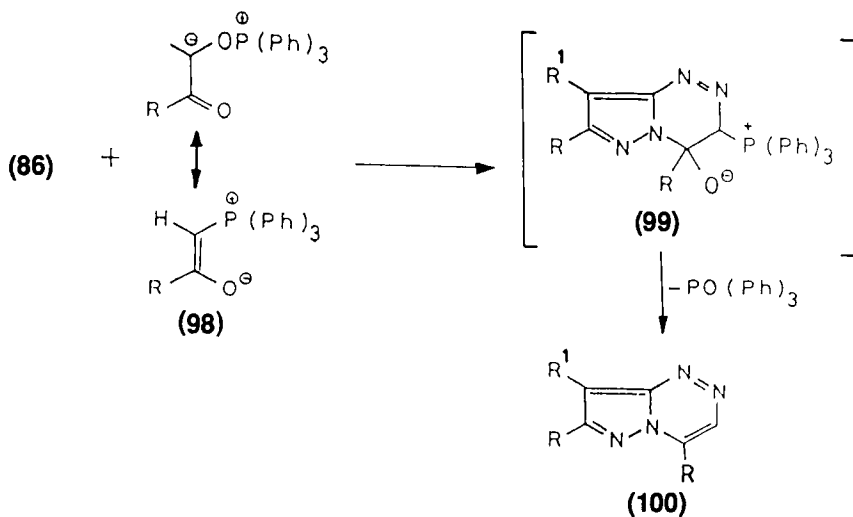
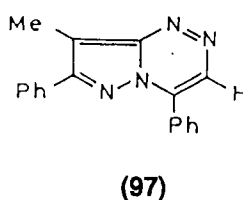
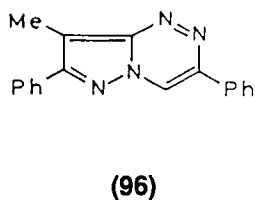
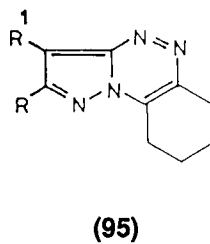
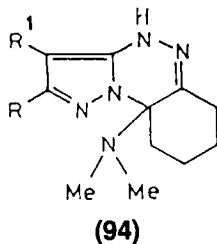
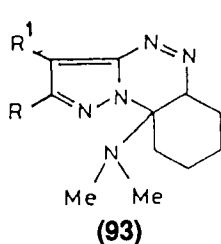
pyrazolotriazines (84), whereas acyclic hydrazones **88** were obtained upon coupling **82** with malononitrile, ethyl cyanoacetate, and benzoylacetonitrile (cf. Scheme 12). These hydrazones (**88**) were cyclized into pyrazolo[5,1-*c*]-1,2,4-triazines (**90a-c**) upon treatment with acidic or basic reagents. Since the coupling reaction is carried out in buffered media, the theory that the acid eliminated during coupling catalyzed the cyclization was ruled out. Elnagdi *et al.* [78ZN(B)218] assumed an equilibrium between **82** and diazobetaine **86** exists, and that **86** underwent cycloadditions with phenols and with the enolates of β -diketones and β -ketoesters, directly affording pyrazolo[5,1-*c*]-1,2,4-triazines. This betaine (**86**) could be isolated and reacted with acrylonitrile and with ethyl acrylate, which would yield **87** (cf. Scheme 12 and 13) [77JA633; 77S556; 78ZN(B)218; 83AP713; 83JOC2330]. Addition of the betaine to 2-aminocrotononitriles has also been reported to yield **89** (76JOC3781). Addition of diazopyrazoles to enamines, ynamines, and vinyl ethers has been reported to yield **91** and **92** (77S556; 83JOC2330).

The mechanism of adding electron-rich systems to diazopyrazoles has been discussed by Padwa and Kumagai (81TL1199). Although they were unable to isolate intermediates in a pure state, the two isomeric intermediate species were characterised by ¹H-NMR during the reaction of 1-dimethylaminohexene with diazopyrazoles such as **93** and **94**. Padwa *et al.* (83JOC2330) suggested that 4 + 2 cycloaddition yielded adduct **93**, which tautomerized to **94** then underwent a 1,4-hydrogen elimination to afford the final isolable **95**. However, the data presented cannot rule out a possible two-step mechanism via cyclic Zwitterionic species.



SCHEME 12

The orientation on addition of asymmetric electron-rich olefins has also been studied by Padwa *et al.* (83JOC2330). Only one regioisomer could be isolated from such reactions. These reactions were assumed to be products resulting from the attachment of the olefinic electron-rich moiety to the exocyclic nitrogen. This assignment was based on ¹H-NMR, which revealed the triazine H-4 in **96** at δ 8.5. This, however, does not rule out isomeric **97**, as Ege and Gilbert (81JHC675) reported a shift of 8.7 for H-3 in a system believed to be a 3-unsubstituted-4-arylpyrazolo[5,1-*c*]-1,2,4-triazine (Scheme 13).

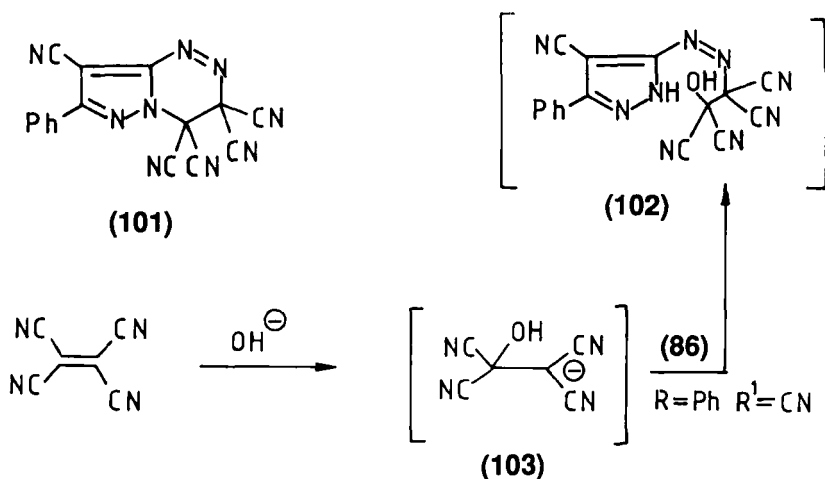


SCHEME 13

Acyltriphenylphosphonium methylides (98) react with **86** in an 8 + 2 cycloaddition to afford intermediate **99**. This then loses triphenylphosphine oxide to yield **100**. $^1\text{H-NMR}$ was utilized to elucidate structure **100**: Ortho protons in **100** were deshielded; R = Ph was taken as support.

If, however, the data reported for H-3 in this system is compared to that reported for H-4 in **96**, one can realize that relying only on $^1\text{H-NMR}$ for elucidating structures of derivatives of pyrazolo[5,1-*c*]-1,2,4-triazines may be misleading (81JHC675).

Elnagdi *et al.* (88AP851) found that the reaction of **86** with tetracyanoethylene does not afford the expected structure **101** ($X = Y = \text{CN}$). Instead the hydrazones (**88**) ($X = \text{R}^1 = \text{CN}$; $\text{R} = \text{Ph}$) were isolated. Similarly, compounds **88** were formed upon treatment of **86** with cinnamitrile derivatives. It was thus postulated that the reaction of these electron-poor double bonds with **86** proceeded via formation of an acyclic intermediate (e.g. **102**) by reaction with **103**, which then decomposes into isolable **101** by the elimination of water. In support, compounds **86** were recovered unreacted when treated with cinnamitriles or with tetracyanoethylene in the absence of water (88AP851).

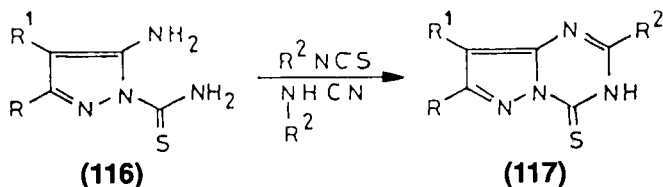


A variety of substituted aminopyrazoles have been diazotized and reacted with active hydrogen compounds. Intermediate hydrazones that were cyclized into pyrazolo[5,1-*c*]-1,2,4-triazines, are isolated in some cases [76JMC517; 79ZN(B)275; 82MI1, 82MI2; 83AP241, 83AP713, 83IJC(B)552; 84PHA432; 85KGS682, 85MI1, 85MI3, 85PHA(40)176; 89CC1082]. Gray, Stevens, and Stevens [78JCS(PI)885] reported the preparation of 3,4-diphenylpyrazolo[5,1-*c*]-1,2,4-triazin-7-amine via reacting 3-hydrazinopyrazol-5-amine with benzil. However, since the latter hydrazone was prepared by reacting malononitrile with hydrazine, the identity of the starting product needs to be confirmed. Taylor and Hartke (59JA2452) established earlier that the reaction of malononitrile with hydrazine affords 5-amino-2-cyanomethylpyrazole-4-carbonitrile.

2. *Pyrazolo[1,5-a]-1,3,5-triazines (72)*

Most reported syntheses of derivatives of **72** utilize aminopyrazoles as starting materials [73SZP7257173, 75HCA761, 75JHC893, 75USP3910907; 76EGP123468, 76PHA546; 77ZN(B)430; 79EUP4171, 79JOC4547; 80SAP7901138; 82JMC243; 83H2437; 84JHC389, 84JHC781; 85JHC601]. Thus, alkyl and arylpyrazolo[1,5-*a*]-1,3,5-triazines (**114**) are prepared via reaction of **81** with amidines and subsequent cyclization of product **111** with orthoesters. Similarly, 2,4-diaminopyrazolo[1,5-*a*]-1,3,5-triazine (**106**) is formed upon refluxing **81** with dicyandiamide in aqueous acid; **108** or **109** are likely intermediates (57G597). 2,4-Dioxypyrazolo[1,5-*a*]-1,3,5-triazines (**113**) are produced either by cyclization of **115** via reacting of **81** with ethoxycarbonyl isocyanate or via condensing **81** with dichloroformylamine (Scheme 14) (79EUP4171; 79GEP2900288; 80SAP7901138).

2-Thioxopyrazolo[1,5-*a*]-1,3,5-triazines (**104**) are prepared by cyclization of thiourea (**107a**) produced by reacting **81** with ethoxycarbonyl isothiocyanate (84JHC389). Cyclization of **107b** afforded **105** [77ZN(B)430]. 7-Oxypyrazolo[1,5-*a*]-1,3,5-triazines (**112**) are prepared by reacting **81** with formyl urethane and cyclizing the resulting product **110** (76JHC1305).



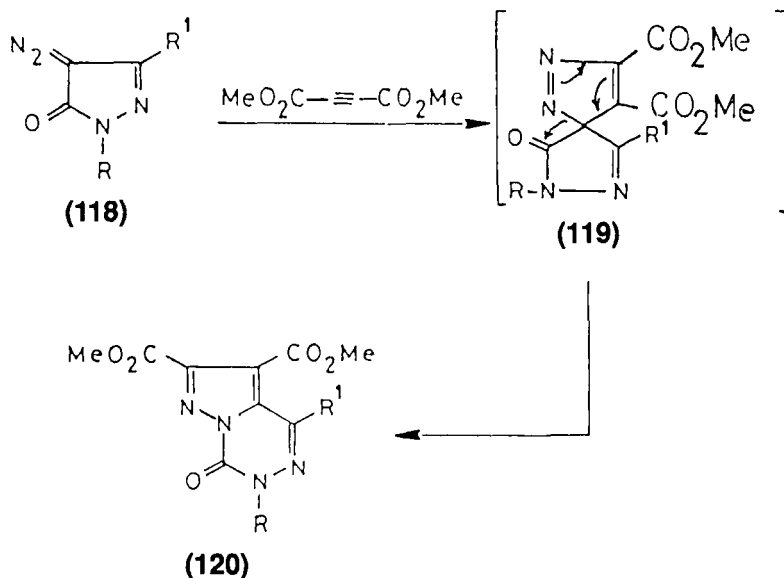
The reaction of **116** with isothiocyanates or with substituted cyanamides gave **117** (76PHA546; 83EGP203546). Diarylpyrazolo[1,5-*a*]-1,3,5-triazines were prepared by reacting 3(5)-aminopyrazole with monothiodiacylamines or *N*-aroylthioimides (85JHC7). 3(5)-Aminopyrazole methanesulfonate reacts with cyanoguanidine to yield 2,4-diaminopyrazolo[1,5-*a*]-1,3,5-triazines (79GEP2900288). The reaction of one-substituted 5-anilinympyrazole with primary amines and formaldehyde in methanol solutions at room temperature afforded 1,2,3,4-tetrahydropyrazolo[1,5-*a*]-1,3,5-triazines (88JHC1387).

Pyrazolo[1,5-*a*]-1,3,5-triazines are also obtained from acyclic intermediates. Thus, treatment of cyanoethanoic acid hydrazide with benzoyl isothiocyanate affords the corresponding benzoylthiosemicarbazide, which cyclizes into 4-thioxo-2-phenyl-3,4,6,7-tetrahydropyrazolo[1,5-*a*]-1,3,5-triazine-7-one upon treatment with 5% potassium hydroxide (84JHC781).

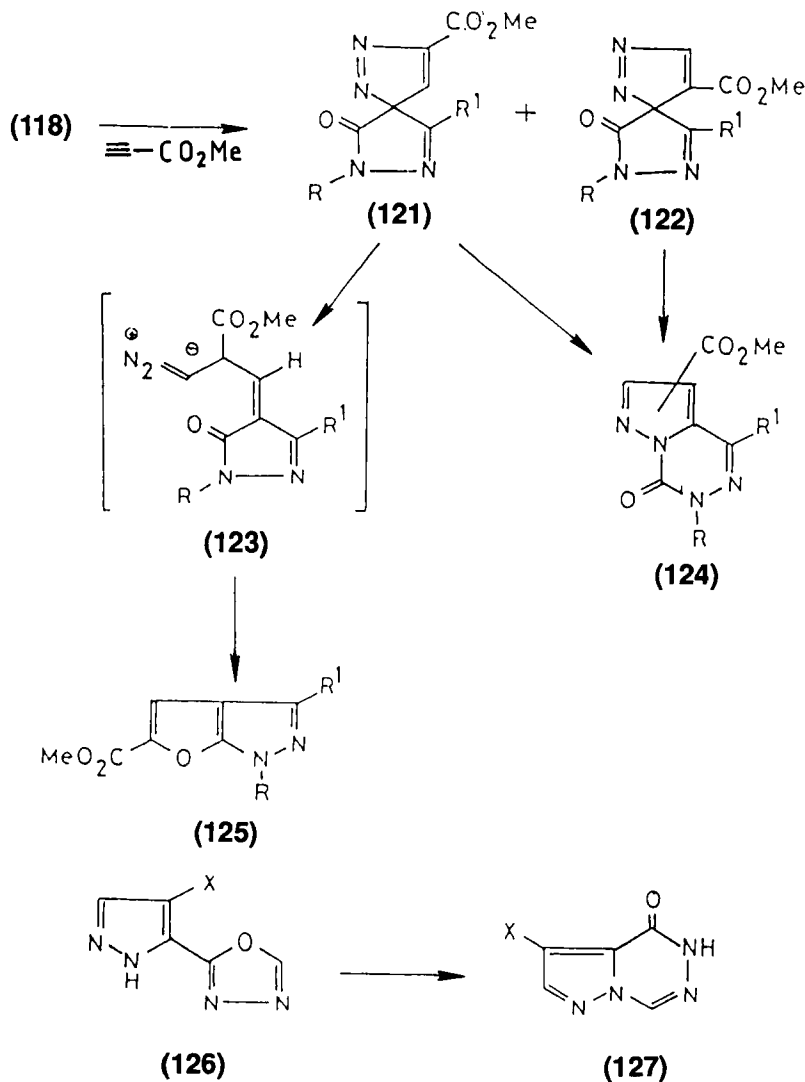
3. *Pyrazolo[1,5-*d*]-1,2,4-triazines (73)*

The reaction of 4-diazopyrazoles (**118**) with dimethyl acetylenedicarboxylate affords pyrazolo[1,5-*d*]-1,2,4-triazin-7-ones (**120**), which result from dipolar cycloaddition followed by a Van-Alphen Hutter rearrangement of the initially produced spiro-3*H*-pyrazole adduct (**119**) (83JOC1069) (Scheme 15). The reaction of **118** with unsymmetrical acetylenic esters afforded variable mixtures of regioisomeric pyrazolo[1,5-*d*]-1,2,4-triazines (**124**) and 1*H*-furo[2,3-*c*]pyrazoles (**125**). Product formation is rationalized in terms of a substituent-dependent partitioning between spiropyrazole adducts **121** and **122**, and ring opened diazoalkenes **123** (82TL2167; 83JOC1069) (Scheme 16). The rearrangement of oxadiazole **126** affords **127** (82JHC817).

A convenient route to pyrazolo[1,5-*d*]-1,2,4-triazines utilizing pyrazol-5-carbohydrazone (**128**) has been reported (55JA1148). Thus, **128** $R^1 = H$, afforded pyrazolo[1,5-*d*]-1,2,4-triazine (**131**) on treatment with orthoesters, probably via acyclic intermediate **130**. Treatment of **128** with orthoesters afforded mesoionic **129** (Scheme 17) (80JHC1291). Treatment of 4-ribosylpyrazol-5-aldehyde ethoxycarbonylhydrazone with cesium carbonate afforded *C*-ribosylpyrazolo[1,5-*d*]-1,2,4-triazin-4-one (83MI1).

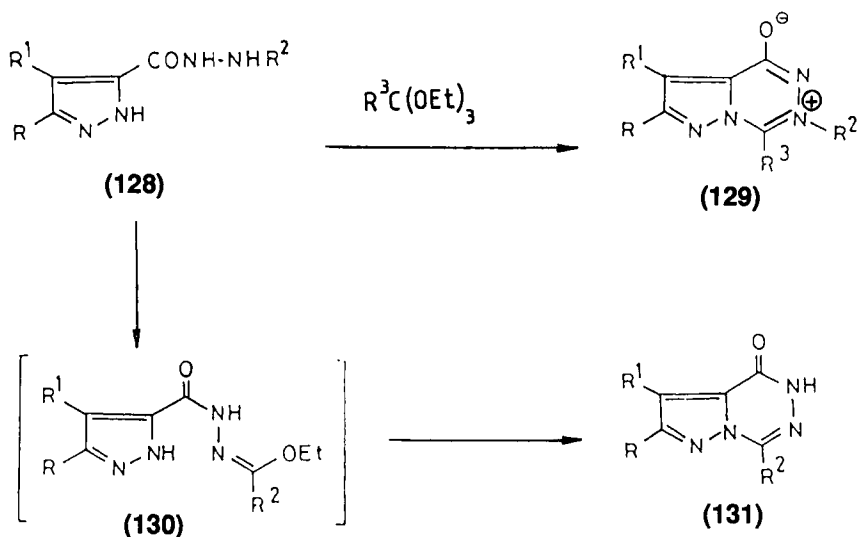


SCHEME 15



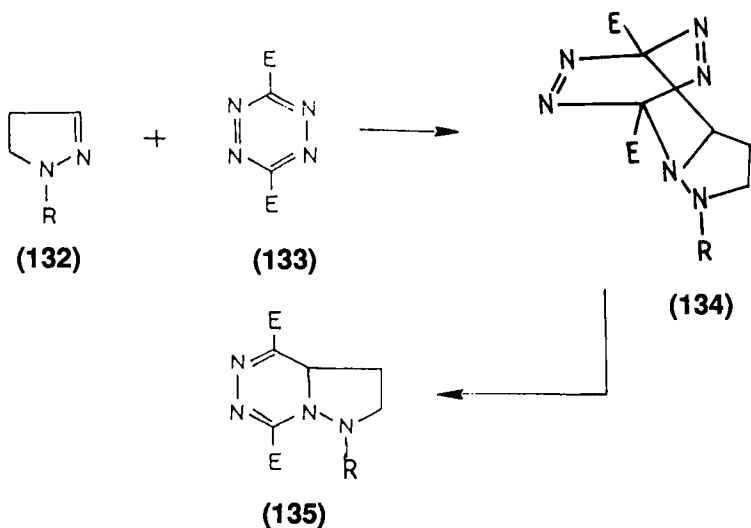
SCHEME 16

Seitz and co-workers (84AP237) reported that 2-pyrazolines (132) react with tetrazines (133) to yield pyrazolo[1,5-*d*]-1,2,4-triazines (135), most likely via intermediate cycloadduct 134 (Scheme 18). Addition of pyrazoles to 133 has been reported to also yield pyrazolo[1,5-*d*]-1,2,4-triazine derivatives (88CZ17).

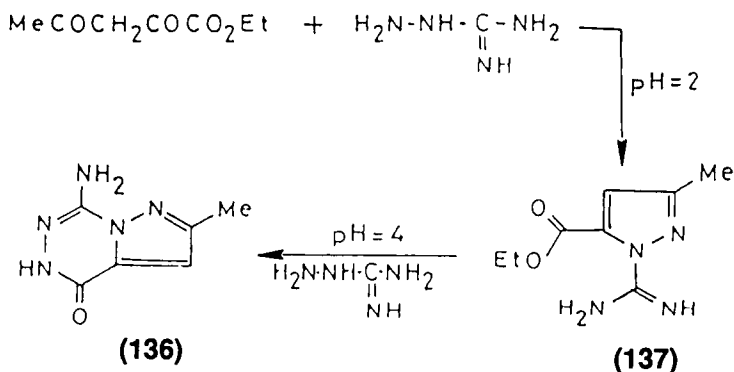


SCHEME 17

The reaction of aminoguanidine with ethyl 2,4-dioxopentanoate afforded pyrazole **137** at pH 2. When the reaction was carried out at pH 4, pyrazolo[1,5-*d*]-1,2,4-triazine (**136**) was formed upon further reaction of **137** with aminoguanidine (76M12) (Scheme 19).



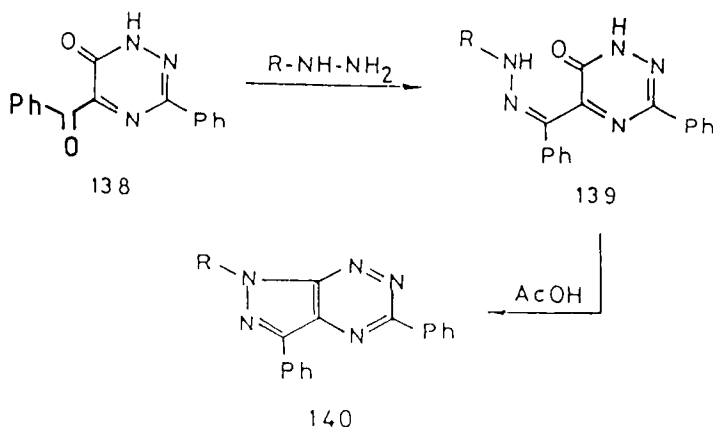
SCHEME 18



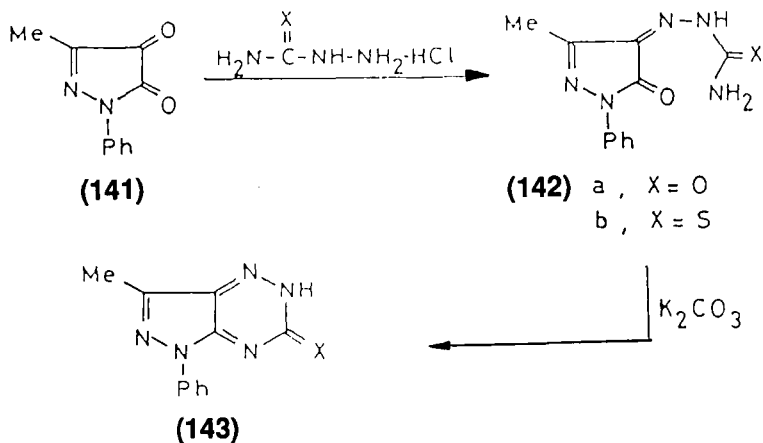
SCHEME 19

4. Pyrazolo[3,4-e]-1,2,4-triazines (74)

Only a limited number of derivatives of this ring system have been reported in literature. The only efficient synthesis utilized azoaroyl-1,2,4-triazines. Thus, condensation of **138** with hydrazines afforded the hydrazones (**139**), which give **140** on reflux in acetic acid [85MI2, 85PHA(39)504] (Scheme 20). It has been reported that derivatives of **74** were synthesized by cyclization of pyrazoline-4,5-dion-4-isothiosemicarbazones and 4-amidinohydrazones in phenol at 180–200°C (88JPR57).



SCHEME 20

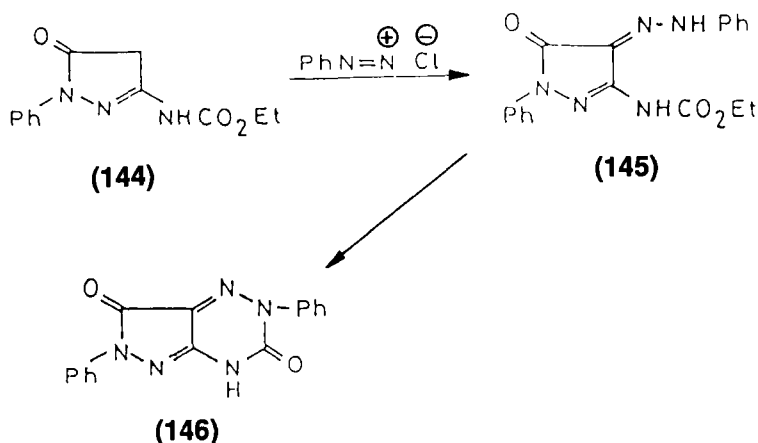


SCHEME 21

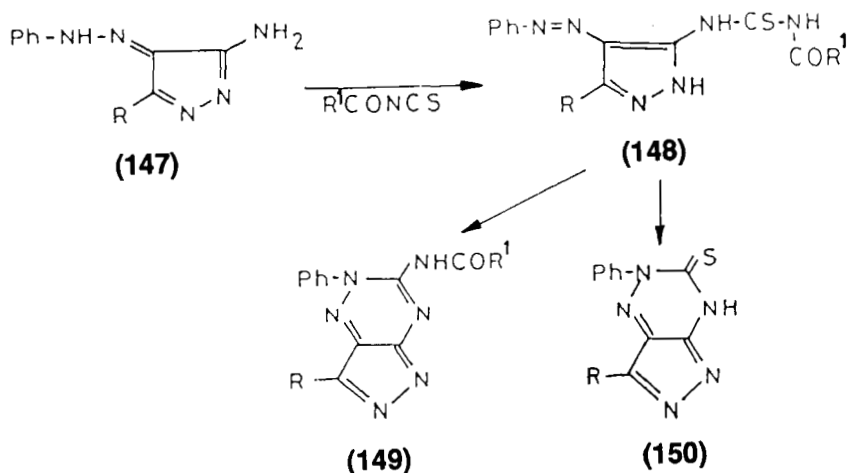
5. Pyrazolo[4,3-*e*]-1,2,4-triazines (**75**)

Several routes to pyrazolo[4,3-*e*]-1,2,4-triazines have been reported. Thus, treatment of pyrazolidine-4,5-dione (**141**) with semicarbazide hydrochloride or with thiosemicarbazide in cold ethanolic sodium carbonate afforded the corresponding carbazones (**142a**) or thiosemicarbazones (**142b**), which cyclized into pyrazolo[4,3-*e*]-1,2,4-triazines (**143**), upon treatment with potassium carbonate (Scheme 21) (84JHC923, 84JPR994).

Another approach to synthesizing pyrazolo[4,3-*e*]-1,2,4-triazines is by coupling ethoxycarbonylpyrazolones with aryldiazonium salts and subsequently cyclizing the resulting hydrazones; e.g., the formation of **146** from **144** via **145** (76MI1).



Similarly, hydrazones **148** (prepared via reaction of **147** with aroyl or with ethoxycarbonyl isothiocyanates) afforded **149** or **150** upon cyclization under various conditions [77ZN(B)430; 79ZN(B)275].



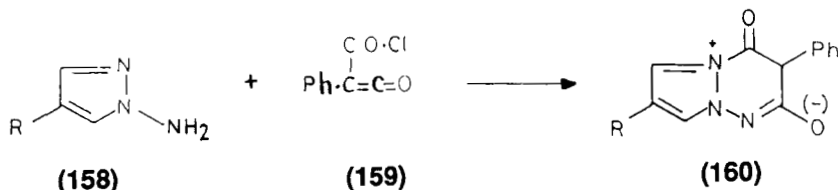
The reaction of aromatic amines with tetrazine (**151**) gave either 1,2,4-triazoles (**154**) or pyrazolo[4,3-*e*]-1,2,4-triazines (**155**), depending on the substituents. While aniline, *p*-toluidine, *p*-anisidine and *p*-chloroaniline afford **155**, the bromo and *p*-nitro derivatives give **154**. Intermediates **152** and **153** were postulated (Scheme 22) (82CB683).

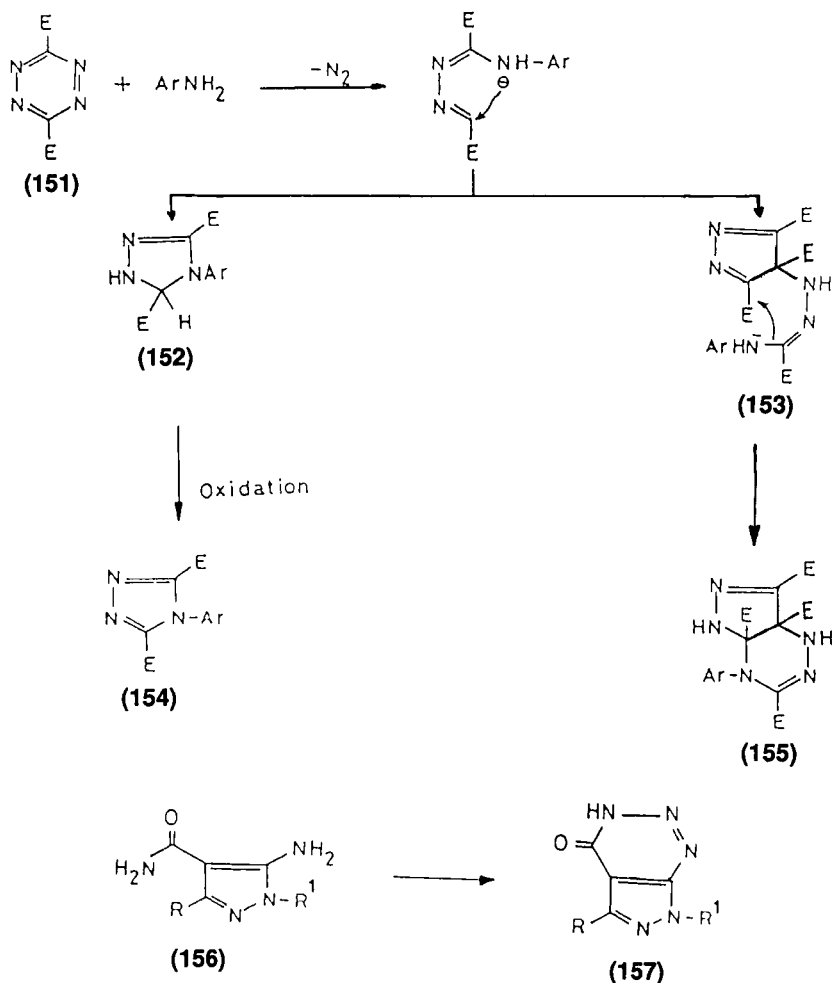
6. Pyrazolo[4,3-*d*]-1,2,3-triazines (77)

These are generally obtained by diazotization of 5-aminopyrazole 4-carboxamides, e.g., conversion of **156** to **157** (38G49; 59GEP1058519; 83EUP127028; 86JMC1544).

7. Pyrazolo[1,2-*a*]-1,2,3-triazines

The only reported derivative of this ring system (**160**) is prepared from **158** and **159** (83H1271). Only mesoionic derivatives of this ring system can be considered aromatic.





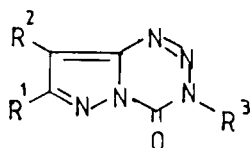
SCHEME 22

In other pyrazolotriazines, to our knowledge, derivatives of 77–80 have not yet been prepared.

D. SYNTHESIS OF PYRAZOTETRAZINES

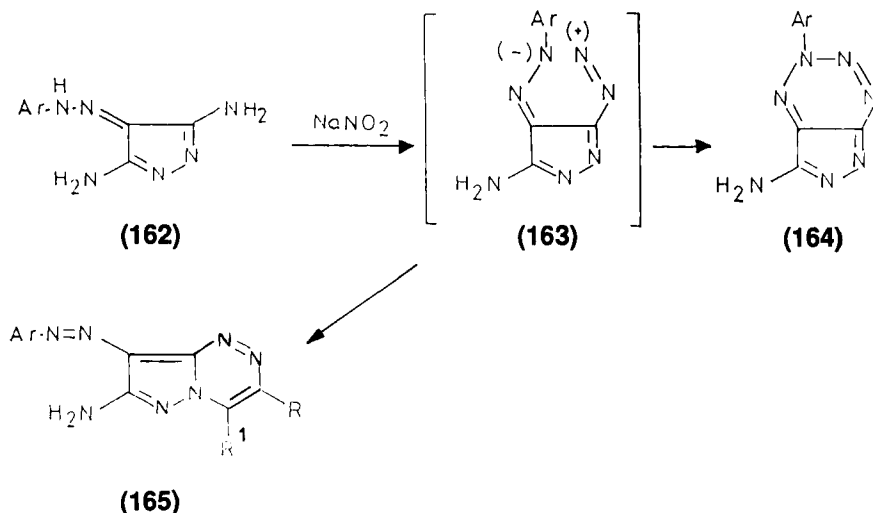
Derivatives of two pyrazolotetrazine ring systems have been synthesized. Thus, the pyrazolo[5,1-*d*]-1,2,3,5-tetrazine derivative (161) was formed up on reacting diazopyrazole (86) with isocyanates (79TL4253).

Alternatively, diazopyrazole (**86**) reacted with amines to yield triazines which, when treated with activated carbonic acid derivatives, e.g., phosgene, afforded derivatives of **161** (87CB1375).



161

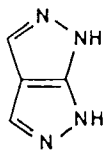
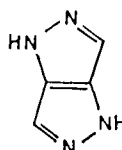
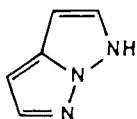
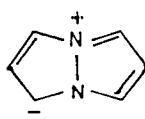
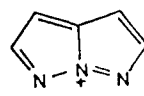
Pyrazolo[3,4-*e*]-1,2,3,4-tetrazine (**164**) was formed by intramolecular cyclization of **163**, prepared via diazotization of **162** [79ZN(B)275; 80MI1]. The intermediacy of **163** has been established via isolating coupling products of **163** with different CH acidic reagents, yielding **165**.



III. Synthesis of Pyrazoles Condensed to Five-Membered Rings

A. SYNTHESIS OF PYRAZOLOPYRAZOLES

Three systems (**166**, **167**, and **168**) are aromatic 10π electron systems. Mesoionic derivatives of **169** are aromatic as are salts of **170**. In the following sections we describe synthetic routes to ring systems whether or not the products are aromatic 10π electron systems.

**(166)****(167)****(168)****(169)****(170)**

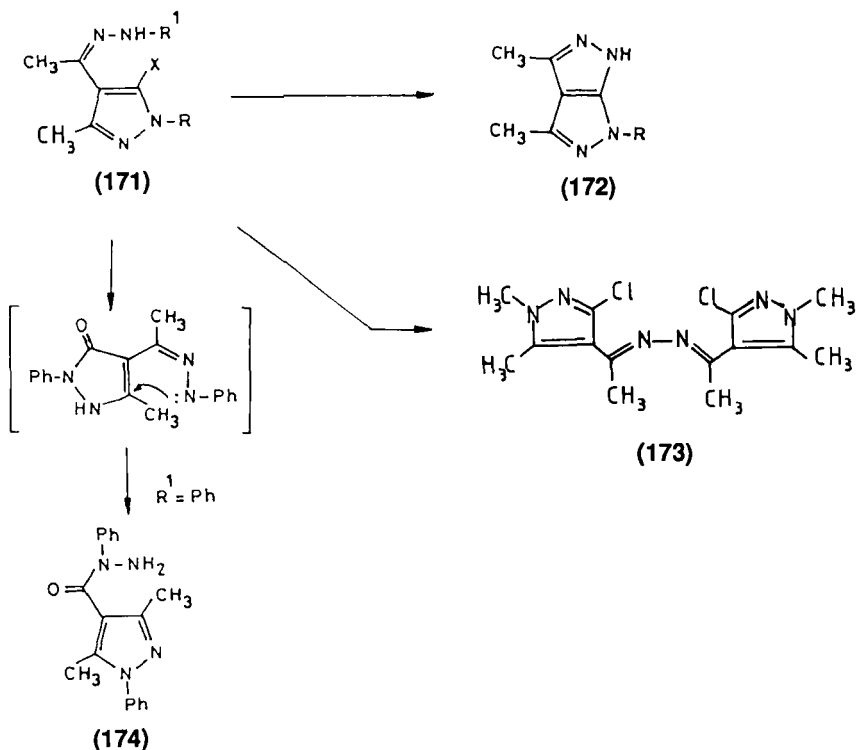
1. *Pyrazolo[3,4-c]pyrazoles (166).*

Ghosh and Das-Gupta (39JIC63) claimed the isolation of **172** up on cyclization of **171**. However, Gonzales and Elguero have shown that this cyclization does not occur when the pyrazole is an *N*-methylated derivative or when the hydrazones are phenylhydrazones (86JHC999). Heating the phenylhydrazone (**171**) ($R^1 = \text{Ph}$, $R = \text{CH}$) in acid afforded azine **173**. When **171** ($R = R^1 = \text{H}$ or CH_3 , and $X = \text{Cl}$) is heated under the same conditions, hydrazide (**174**) is formed (78MI1). The formation of **174** is assumed to proceed as shown in Scheme 23.

5-Chloro-4-(2-chlorobenzoyl)-1-phenyl-3-methylpyrazole yields 1-phenyl-4-(2-chlorophenyl)-3-methylpyrazole upon treatment with hydrazine (17CB737). Other derivatives of pyrazolo [3,4-*c*] pyrazoles have been similarly prepared (22CB291).

2. *Pyrazolo[4,3-c]pyrazoles (167)*

Pyrazolo[4,3-*c*]pyrazole (**177**) is prepared by reducing **175** with disodium dithionite and diazotizing the resulting amine (74BCJ1039). The synthesis of other derivatives by a similar approach has been reported (08CB3849; 60MI659; 73TL1199; 74BCJ1493; 77JHC1107). Elnagdi *et al.* [82JCS(PI)989] reported the formation of **181** from **178** and α -chloroacetylacetone or ethyl α -chloroacetoacetate via hydrazonyl chloride (**179**). However, it was later shown that **180** is the intermediate. The exact mechanism is still unclear (Scheme 24) [89ZN(B)951]. A synthesis of

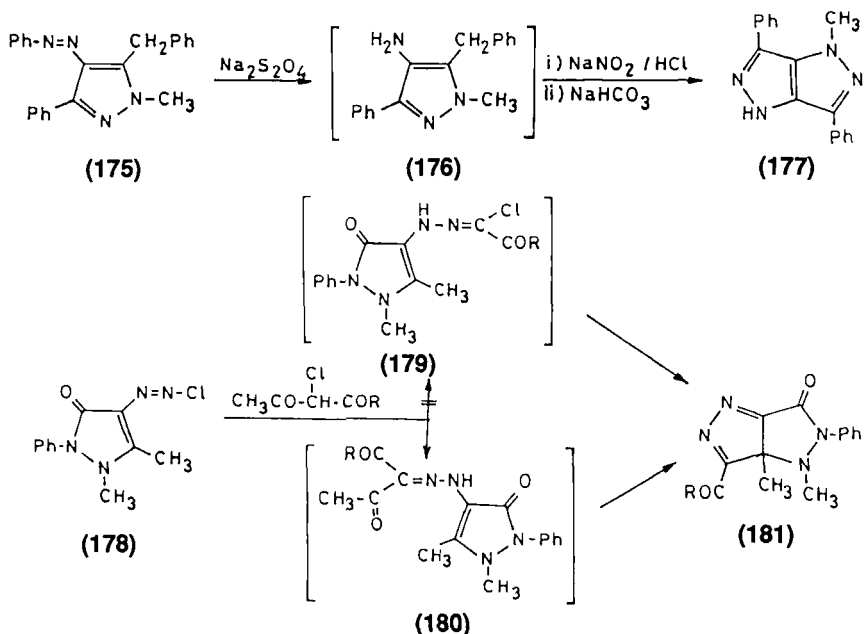


SCHEME 23

2,5-diphenyl-6-imino-2,3,4,5-tetrahydropyrazolo[4,3-*c*]pyrazol-3-one form ethyl 3-cyano-2,3-diphenylhydrazonobutanoate has been reported (34LA97). Arylazoethynylarenes give pyrazolo[4,3-*c*]pyrazoles upon heating in solution (69CC1393).

3. *Pyrazolo[1,2-*a*]pyrazoles (168)*

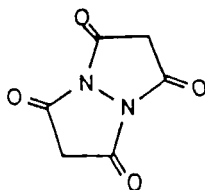
Three main routes to pyrazolo[1,2-*a*]pyrazoles are known. The oldest employs malonic acid derivatives and hydrazines (11LA27; 32JA3674; 66AP441; 76LA2156; 77AG61; 79CB2609; 80GEP144775; 83CB2714; 83MI4; 86AP537; 86AP646; 86AP70). Thus, 2,4,6,8-tetraoxo-1,4-diazabicyclo[2,2,2]octane (**182**) is obtained upon reacting diethyl malonate with hydrazine hydrate (11LA27). A variety of 3,7-polysubstituted derivatives of **182** were synthesized, from hydrazines with diethyl alkylmalonates (66AP441; 70AP218; 83CB2714; 83MI4; 86AP70; 86AP646). Very similar is the cyclization of *N,N'*-bis(cyanoacetylhydrazide) to 2,5-diamino-



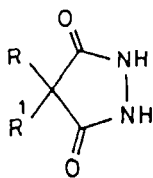
SCHEME 24

3,6-dioxo-1,4-diazabicyclooct-2,5-enes (80GEP2855193). Also, the reaction of carbon suboxide with pyrazoles gives pyrazolo[1,2-*a*]pyrazoles (86CC144).

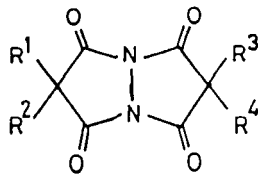
Several pyrazolo[1,2-*a*]pyrazoles are prepared by alkylation of pyrazoles with 1,3-dihalo compounds or with malonyl chloride (66FRP1441519; 82LA420; 86AP70). For example, treatments of **183** with disubstituted malonyl chlorides afford **184**. Very similar to this is the formation of pyrazolo[1,2-*a*]-pyrazolium bromide from 1*H*-pyrazoles and bromomethyloxirane (71JHC489; 79JOC4473).



(182)



(183)



(184)

A simple three-step synthesis of diazabicyclo[3,3,0]octadienes from α -keto esters via pyrazolinones **185** and halopyrazolinones **186** is known

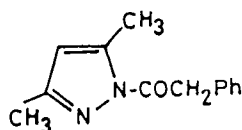
(80MIP1) These findings are in contrast to other reports (84H2523). Treatment of **186** with bases affords a mixture of **191** and **192**. A plausible mechanism involves **186** undergoing hydrogen chloride elimination in the presence of base to yield **187**, which is in equilibrium with **188**. Reaction of **187** with **188** affords a mixture of intermediates **189** and **190**. **190** yields **192**, whereas N_2 elimination from **189** gives **191** (78JA6516; 80JA4983; 80MIP1) (Scheme 25).

1-Allylpyrazole is converted into 1-substituted pyrazolo[1,2-*a*]pyrazole upon treatment with bromine and subsequent cyclization of the formed bromo adduct in refluxing acetone (65JA4393, 65JA5256; 81JOC614). The parent pyrazolo[1,2-*a*]pyrazole ring has been prepared employing this route (65JA528; 66JA5588).

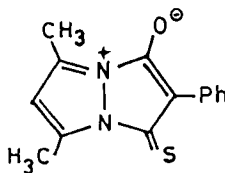
1,4-Diazabicyclopiazoles are formed via reaction of pyrazolium ylides with dipolarophiles. Thus **194**, prepared by reacting **193**, with hexafluoroacetone, reacts with dimethylacetylene dicarboxylate (DMAD) to yield **195**. The reaction of **194** with ethyl propiolate afforded a mixture of **196** and **197** (76LA2156; 76S804; 77AG61; 78CZ152; 79CB2609; 79JPR555; 79JPR565; 79T389). The reaction of **198** with ethynyl ethyl ether afforded **199**. Intermediacy of **200** is postulated. This intermediate was isolated and afforded **201** upon treatment with ethynyl ethers (79T389). Reaction of **200** with methyl propiolate gives a mixture of **201** and **202**. Similar to this work is the formation of **204** upon reacting nitro-olefins with **203** (79JPR555) (Scheme 26). The reaction of **203** with dimethyl maleate gives a mixture of two stereoisomers, **205** and **206**, in a ratio of 2 : 1, while reaction of **203** with dimethyl fumarate gives **205** and **206** in a 1 : 1 ratio (79JPR565).

Formation of pyrazolo[1,2-*a*]pyrazoles via similar criss-cross cycloaddition has been reported (82LA845, 82LA853) (Scheme 27). Synthesis of pyrazolo[1,2-*a*]pyrazoles with azines via criss-cross cycloaddition with electron-rich olefins has been reported [69JCS(D)816].

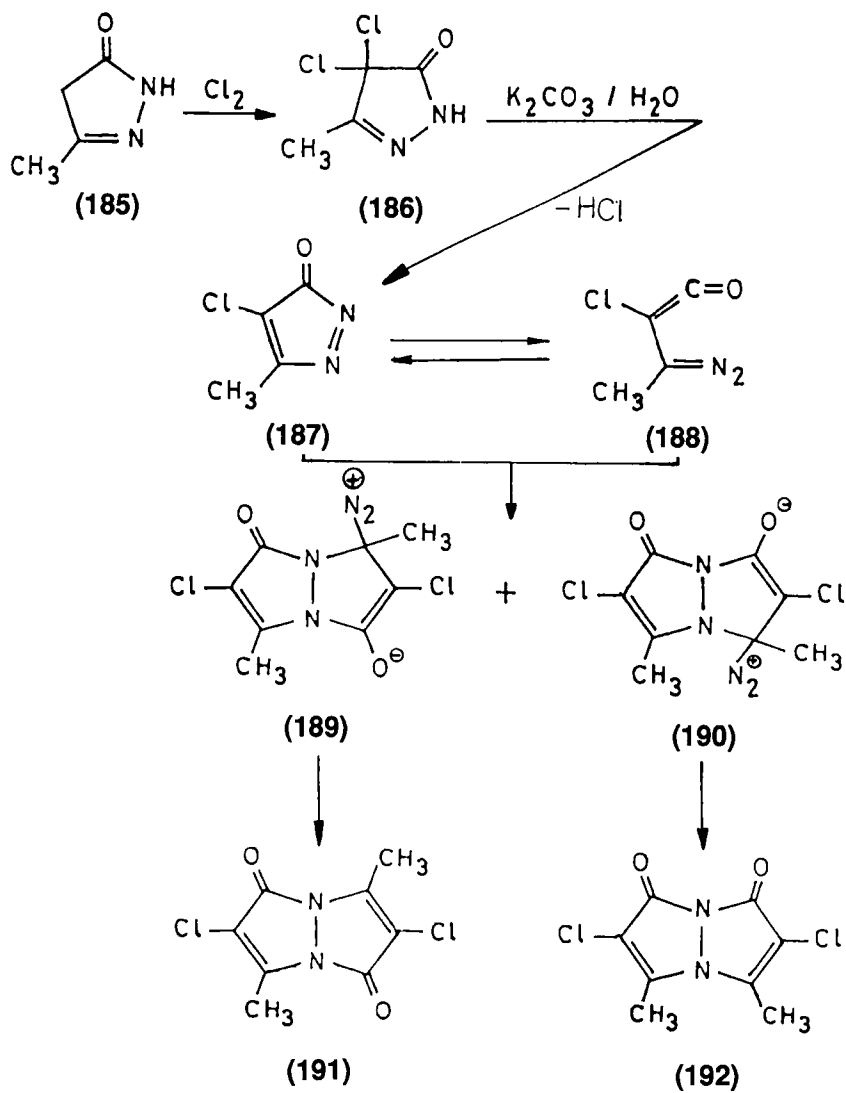
The reaction of pyrazolones (**207**) with 3-oxo-esters gives mainly the pyrazolo[1,2-*a*]pyrazol-1,5-(*1H,5H*) diones (**208**). However, with **207** ($R = Ph$), only oxazines **209** are obtained. Thermal and photochemical isomerization of **204** gives **209** (84CPB930, 84JAP59128384). Phenacetylpyrazole (**210**) is cyclized to **211** with thiophosgene (84JOC3672).



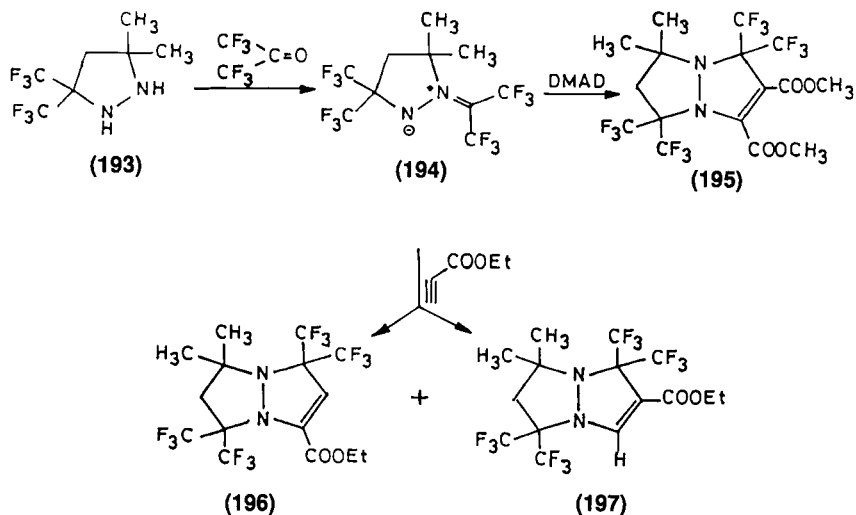
(210)



(211)



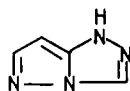
SCHEME 25



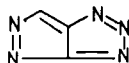
SCHEME 26

B. SYNTHESIS OF PYRAZOLOTRIAZOLES

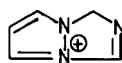
Just six isomeric pyrazolotriazoles are possible (212–217).



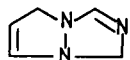
(212)



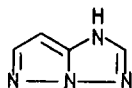
(213)



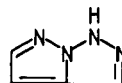
(214)



(215)

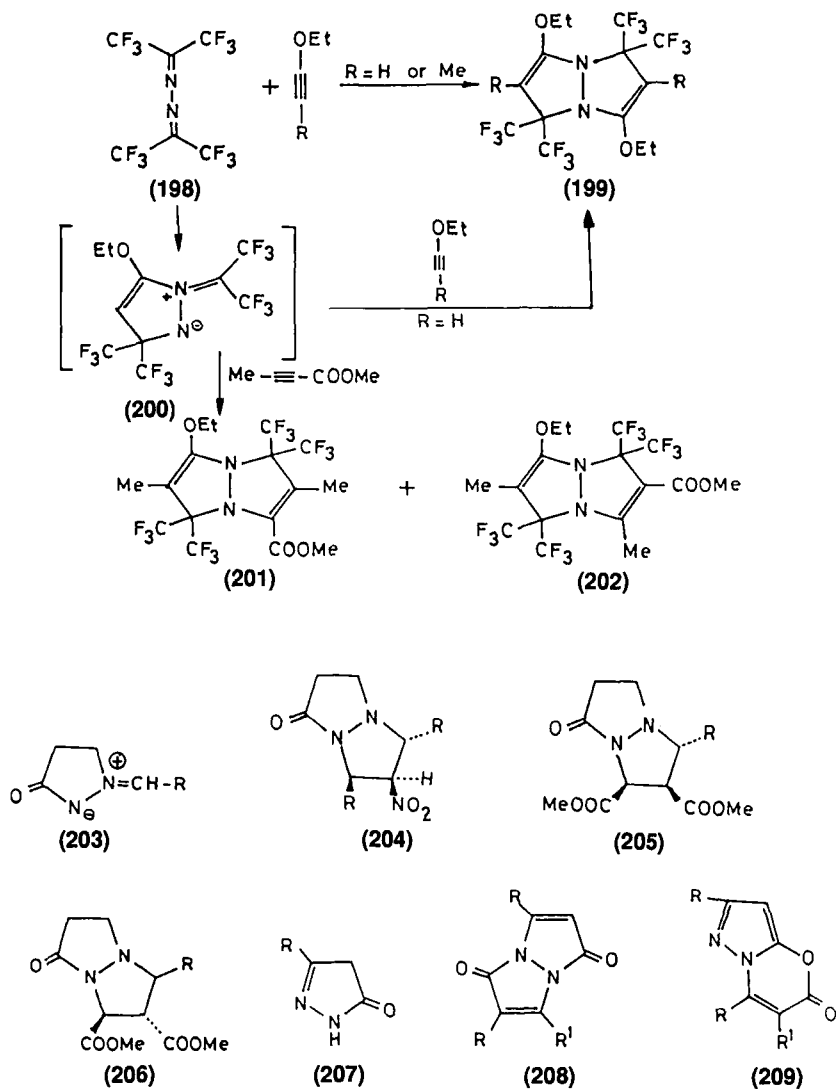


(216)



(217)

Mesoionic derivatives of **214** are also aromatic, and so, synthetic approaches to **214** will be reported. None of the known derivatives of **215** have a 10π electron system, and syntheses will not be reported.



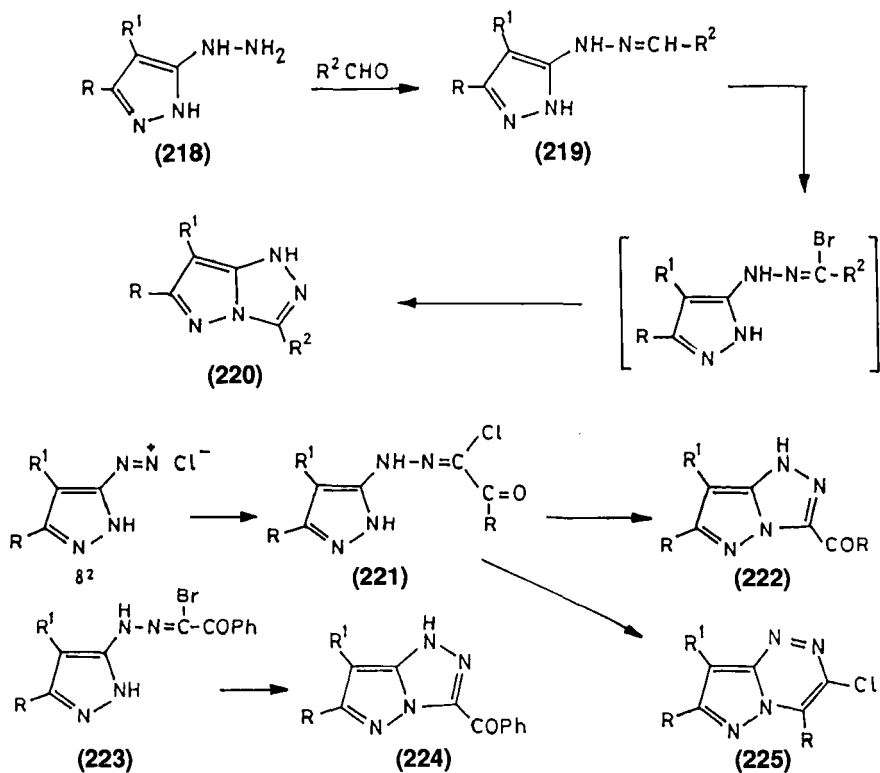
SCHEME 27

1. *Pyrazolo[5,1-c]-1,2,4-triazoles (212)*

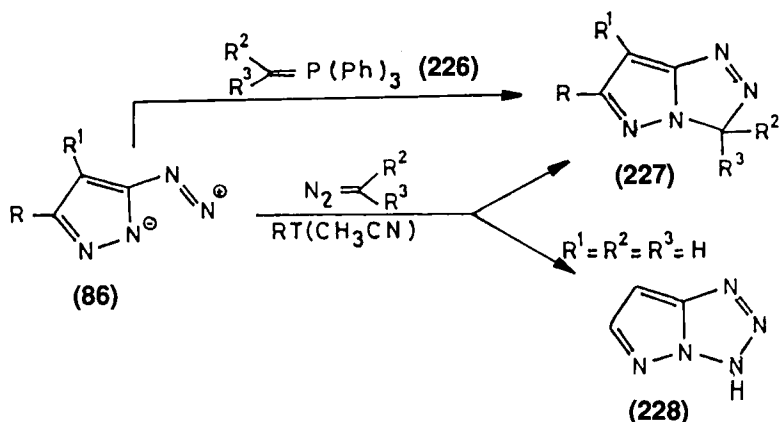
Enormous numbers of derivatives of this ring system have been prepared for use as developers in color photography [70FRP2075583; 71GEP1810462; 73FRP2162518; 76BRP1458377; 76USP4124392; 77CS1;

77JCS(P1)244; 77JCS(P1)2047; 78YZ264; 81EUP34950; 86EUP170164]. Most reported syntheses use 5-hydrazinopyrazoles as starting materials. Thus, condensation of **218** with aldehydes affords the corresponding Schiff bases (**192**). These are cyclized to **220** upon treatment with bromine in acetic acid by means of a hydrazonyl bromide (70GEP1810463; 70FRP2075583; 79MI1).

Elnagdi *et al.* (77JHC227; 80JHC209; 81M245) developed a route to pyrazol-5-ylhydrazonyl chlorides via coupling pyrazole-5-diazonium salts with α -chloroacetylacetone or ethyl α -chloroacetoacetate, yielding **221**. Compounds **221** cyclized readily to **222** upon treatment with triethylamine. This cyclization approach has been used by others [87JHC1341; 87MI1; 87ZN(B)613]. To prepare other substituted pyrazolo[5,1-*c*]-1,2,4-triazoles, Ege and Gilbert cyclized **223** to **224** in the presence of 2-aminopyridine (87MI1). Under the same conditions, **221** affords pyrazolo[5,1-*c*]triazine (**225**) (81M245) (Scheme 28).



SCHEME 28

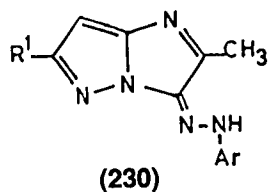
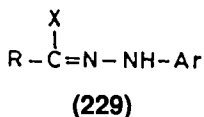


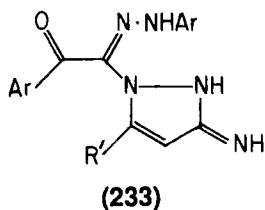
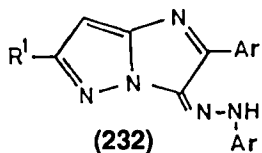
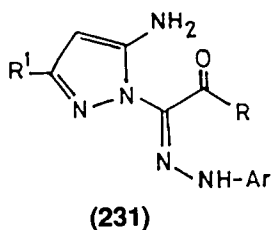
SCHEME 29

The reaction of hydrazinapyrazoles **218** with acid halides also yields alkyl- and aryl-pyrazolo[5,1-*c*]-1,2,4-triazoles. Pyrazolo[5,1-*c*]-triazole-3-thiones are formed from **218** and carbon disulfide [77JCS(P1)2047].

The diazopyrazoles (**86**) react with substituted diazoalkanes to yield **227** in 28–49% yield (79TL1567; 81JHC675; 84CB1726). Diazomethane, in contrast, affords pyrazolotetrazole (**227**) upon treatment with **86** ($\text{R} = \text{Ph}$; $\text{R}^1 = \text{H}$) in 1% yield (70CB3284). Nitrogen is eliminated during formation of **227** from **86**, as shown by N^{15} -labeling experiments. Phosphonium ylides (**226**) also react with **86** in a similar manner to yield **227** (Scheme 29) (79TL1567; 81JHC675).

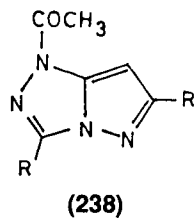
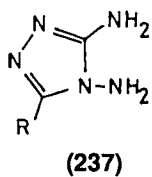
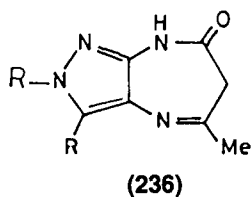
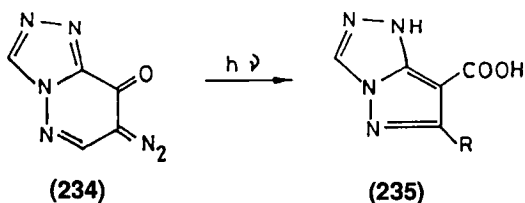
Several reports have been published for the behavior of aminopyrazoles with hydrazidic halides. Thus, Elnagdi *et al.* has reported that 5-aminopyrazoles or 5-pyrazolones react with **229** ($\text{R} = \text{Ar} = \text{Ph}$) to yield pyrazolo[5,1-*c*]-1,2,4-triazoles [82JCS(P1)2663; 84BCJ1650]. Treatment of 5-aminopyrazoles and 5-pyrazolones with **229** ($\text{R} = \text{COCH}_3$) gives alkylation products, some of which cyclize via water elimination to yield imidazo[1,2-*b*]-pyrazoles (**230**) (84BCJ1650). Reaction of 5-aminopyrazoles with **229** ($\text{R} = \text{COPh}$) was reported to yield **232** via intermediate **231** (83JHC639), and a report showed that **233** is also formed (87CB965).



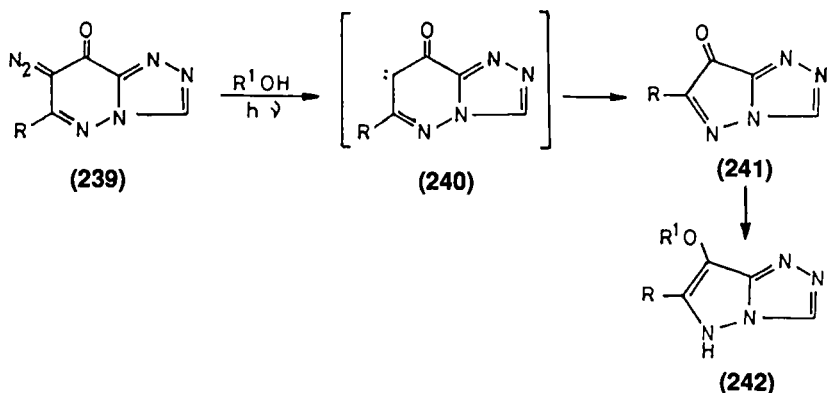


Cyclization of **231** affords **232** (87CB965), which is similar to the findings of Elnagdi and co-workers. (84BCJ1650).

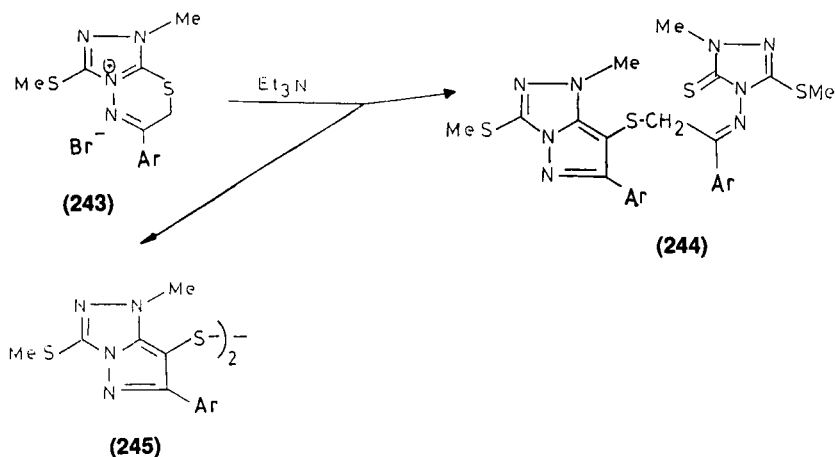
Several pyrazolo[5,1-*c*]-1,2,4-triazoles are obtained by thermal or photochemical isomerization of other heterocycles. Thus, pyrazolo[5,1-*c*]-1,2,4-triazoles (**235**) are prepared via photolysis of **234** (72JPR55). Thermolysis of **236** obtained by condensing **237** with ethyl acetoacetate, gives **238** (74TL23, 74JHC751).



Pyrazolo[5,1-*c*]-1,2,4-triazoles (**242**) are obtained by photochemical Wolf-rearrangement of **239** in ethanol (79JHC195); **240** and **241** are assumed intermediates.



Treatment of **243** with triethylamine yields two compounds that were identified as **244** and **245** by x-ray analysis (85CS230).



2. Pyrazolo[3,4-*d*]-1,2,3-triazoles (**213**)

Derivatives of **213** are obtained either by oxidation of 5-amino-4-arylhydrazonopyrazoles or by diazotization of 4,5-diaminopyrazoles (07LA102; 75JHC279; 77GEP2529688; 80MI1524; 86MI1).

3. Pyrazolo[1,2-*a*]-1,2,4-triazoles (**214**)

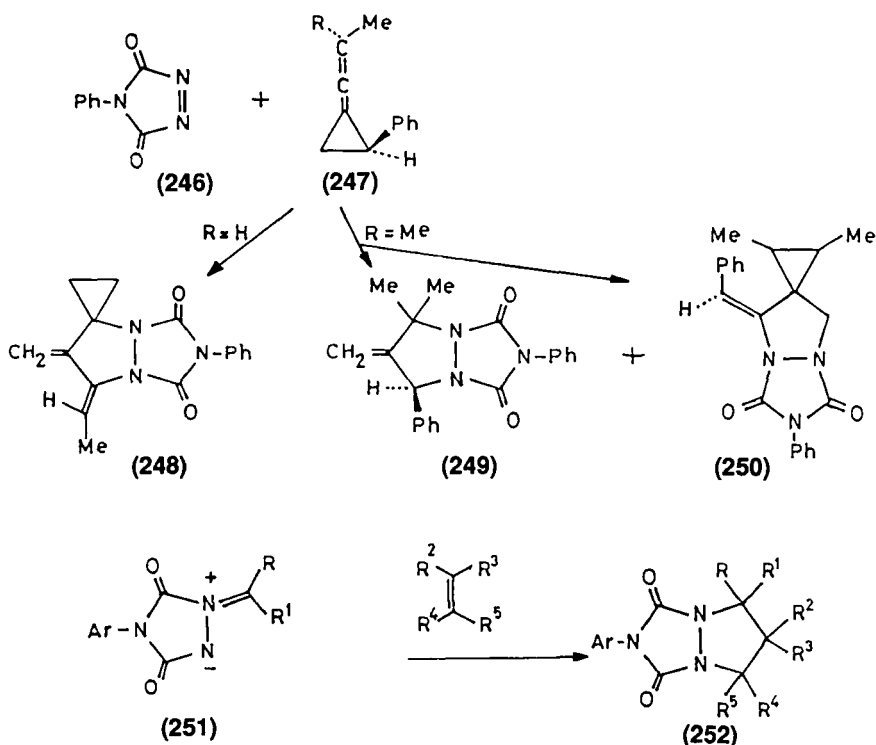
Derivatives of **214** are obtained either from 1,2,4-triazoles or from pyrazoles. Thus, while reaction of **246** with **247** ($R = H$) gives **248**, the

reaction of **247** ($R = \text{Me}$) with **246** gives a mixture of **249** and **250** (73JA1553; 74JA6944).

Alkenylidene cyclopropanes react readily with **246** to yield 1,4-diazo-bicyclo[3,3,0]oxanes, whereas methylidene cyclopropane reacts only very slowly with **246** to yield a 2 + 2 cycloadduct (73AJ1553). Compound **246** also reacts with 5-methylfuran-2(3*H*)-one in an acyl-ene reaction to yield 7-acetyl-6,7-dihydro-2-phenyl-2*H*-pyrazolo[1,2-*a*]-1,2,4-triazol-1,3,5-trione [80JCS(P1)843].

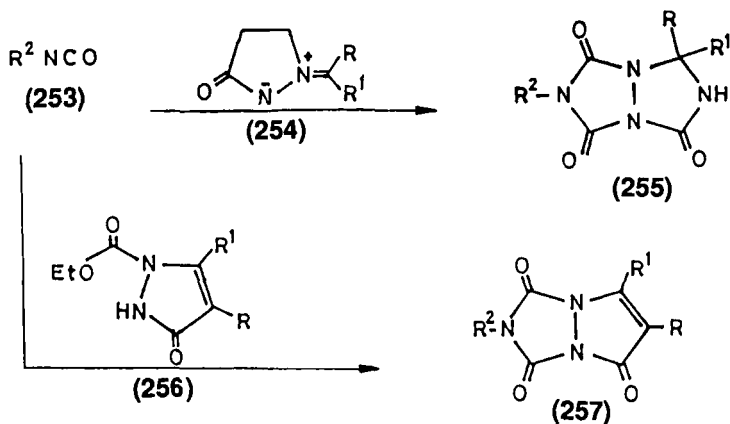
The reaction of aminimide **251** with electron-poor olefins affords pyrazolo[1,2-*a*]-1,2,4-triazoles (**252**) [72ZOR1750; 80JCS(P1)843; 81JOC614] (Scheme 30).

Alkylation of 1,2,4-triazolidines with 1,3-dibromopropane gives 1-(3-bromopropyl) derivatives which are cyclized to pyrazolo[1,2-*a*]-1,2,4-triazoles [79JAP(K)1645]. The syntheses of pyrazolo[1,2-*a*]-1,2,4-triazoles from pyrazole starting materials include the reactions of isocyanates (**253**)



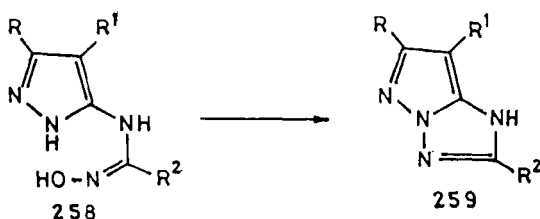
SCHEME 30

with **254** to give **255** and also with **256** to give **257** (65TL2553; 76LA2156; 80GEP3017875; 81LA1361; 82LA845; 82ZOR1986).



4. *Pyrazolo[1,5-*b*]-1,2,4-triazoles (216)*

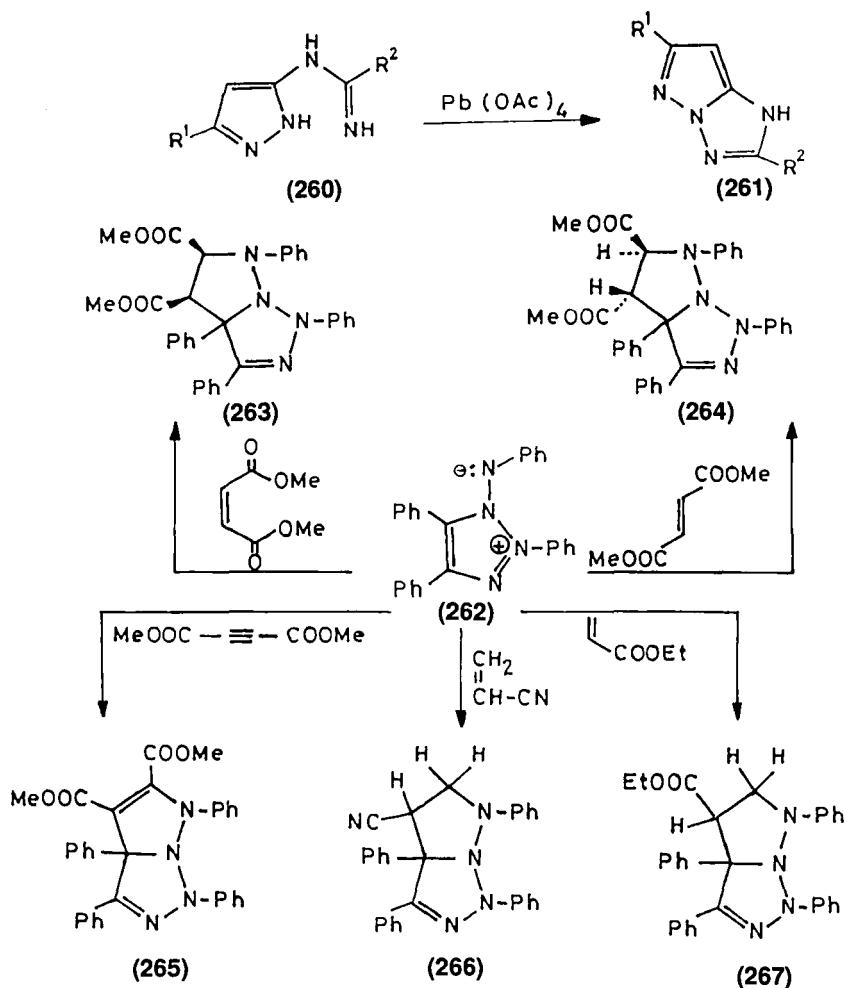
This ring system (**216**) was reported in the mid-1980s [85JAP(K)60197688; 85JAP(K)60190779; 86EUP177765; 86JAP(K)6128947]. Thus, **259**, useful as an intermediate for the preparation of dyes is obtained by intramolecular cyclization of **258** by the action of



p-toluenesulfonyl chloride [85JAP(K)60197688]. Also, *N*-aminotriazoles react with 1,2-diketones to yield derivatives of this ring system (85JAP60190779). Compounds **261**, magneta couplers, and dye developers are prepared by the oxidative cyclization of pyrazole amidines (**260**) (86EUP170164).

5. *Pyrazolo[1,5-*c*]-1,2,3-triazoles (217)*

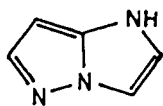
Derivatives of **217** are obtained by reacting **262** with electron-poor olefins (cf. formation of **263**–**267** from **262** in Scheme 31) (71TL633; 72T3987).



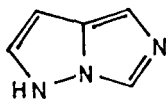
SCHEME 31

C. SYNTHESIS OF IMIDAZOPYRAZOLES

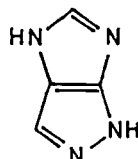
Three isomeric imidazopyrazoles are possible (268–270); all are known. The synthesis of 270 was discussed in the chemistry of the azapentalenes (78AHC183). The best investigated is 268. Derivatives can be obtained from pyrazole intermediates (80JHC877), imidazole intermediates, or via simultaneous synthesis of both ring systems (78MI2). Reaction of



(268)



(269)

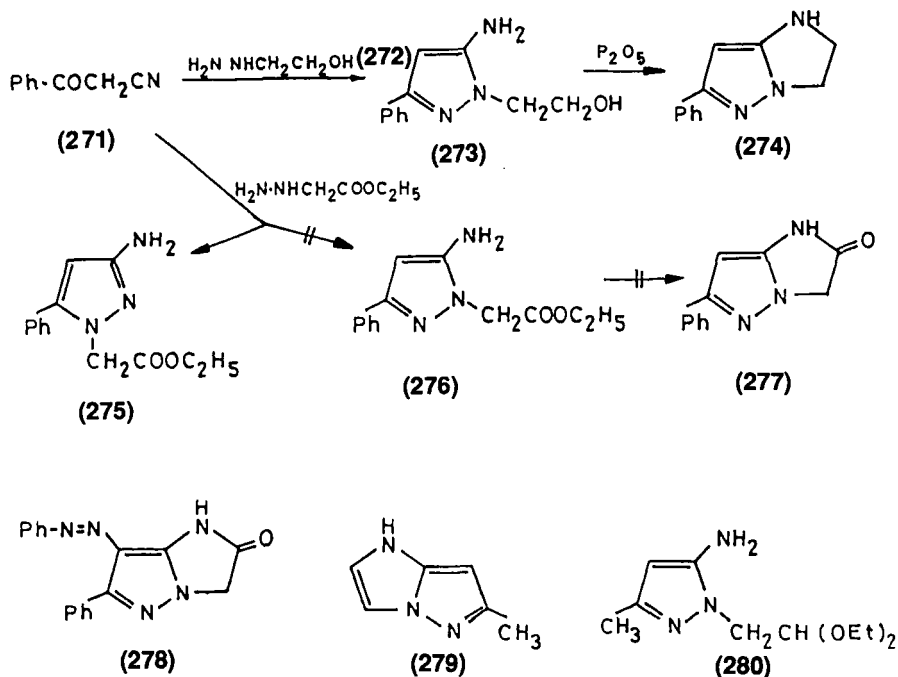


(270)

271 with 2-hydroxyethylhydrazine (**272**) forms **273** which, with phosphorus pentoxide, then gives **274** (75BSF255). Attempted synthesis of **277**, using a similar approach, failed: **272** reacted with ethyl hydrazinoacetate to yield **275** and not **276** (80JHC73). However, the phenylhydrazone of **272** directly gives **278** upon treatment with ethyl hydrazinoacetate.

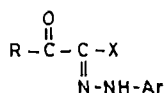
6-Methylimidazo[1,2-*b*]pyrazole (**279**) is prepared via cyclization of **280**. The latter is prepared from 2-aminocrotononitrile and 2-diethoxyethylhydrazine (73JHC411) (Scheme 32).

The reaction of **281** ($R = CH_3$) with aminopyrazoles affords **282** via **283** [82JCS(P1)2663]. Similarly **281** ($R = Ph$), with aminopyrazoles, gives imidazo[1,2-*b*]pyrazoles (83JHC639). Also, **281** ($R = Ph$, $Ar =$ disubstituted

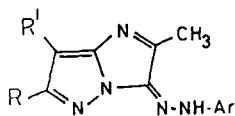


SCHEME 32

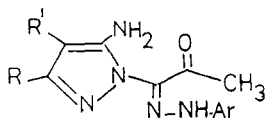
azole) gives **283** and **284** ($R = \text{Ph}$). Attempted cyclization of **283** gives **232** (87CB965). This is similar to a previous report by Shawali, *et al.* (80JHC877). The reaction of **285** with oxalyl chloride gives a mixture of **286** and **287** (84ZOR860). The amination of **285** gives **286**, which was converted into **287**.



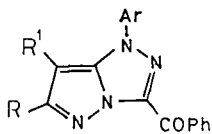
(281)



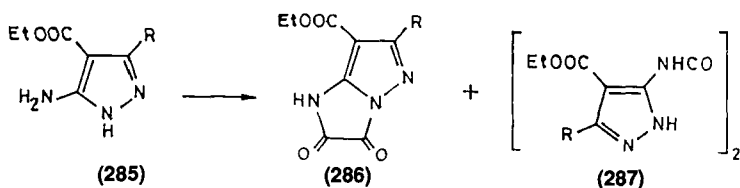
(282)



(283)



(284)

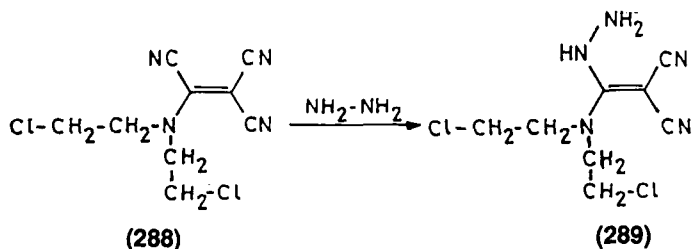


(285)

(286)

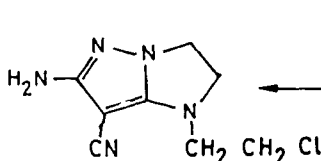
(287)

Simultaneous formation of both rings from acyclic intermediates has been reported (67CB3460; 80JHC73) in the treatment of **288** with hydrazine; **290** probably forms via intermediate **289** (67CB3460).



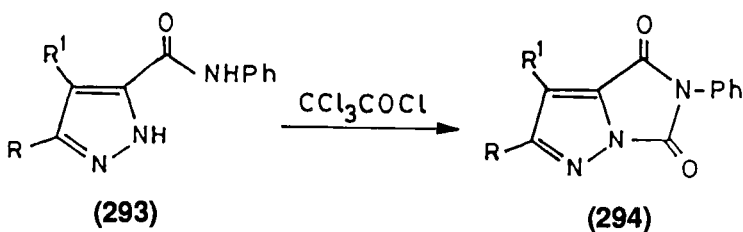
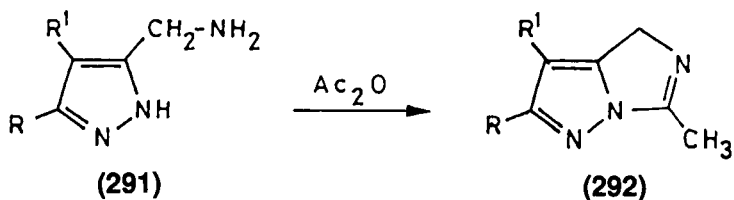
(288)

(289)

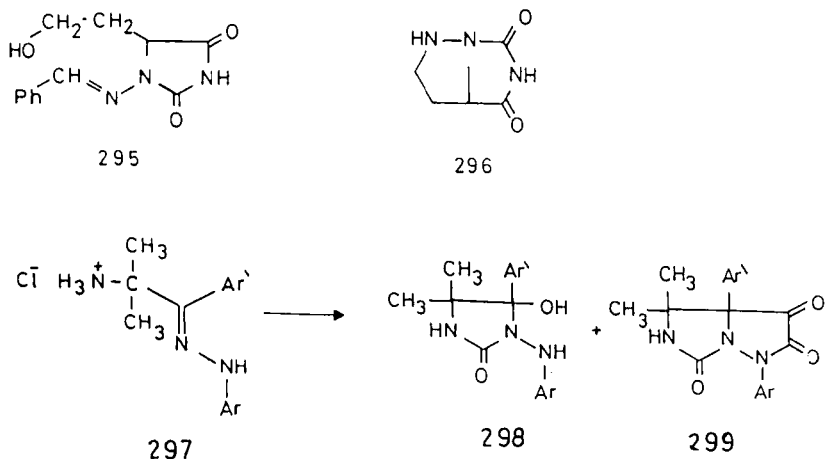


(290)

Derivatives of **269** are formed either via acylation of **291** or by treatment of **293** with trichloroacetyl chloride (cf. **291–292** and **293–294**) (78LA1491; 85JAP6006688).



Imidazo[1,5-*b*]pyrazoles (**269**) have also been prepared from imidazole intermediates. Thus, treatment of **295** with sufonyl chloride gives **296** (69JOC3213). Perhydroimidazo[1,5-*b*]pyrazolones (**299**) are obtained as



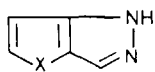
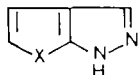
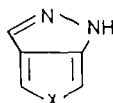
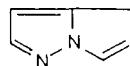
byproducts upon cyclization of **297** with phosgene. The major product in this reaction is **298** (80LA1016).

IV. Other Pyrazoloazoles

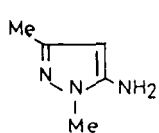
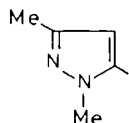
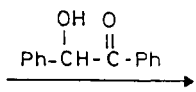
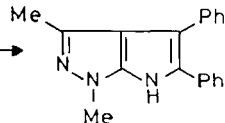
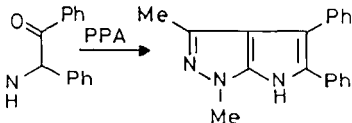
A variety of pyrazoloazoles have been synthesized. Synthetic approaches to these ring systems were summarized by Elguero (78AHC183), and all the reported syntheses of these ring systems that appeared after Elguero's survey are merely extensions of the synthetic approaches summarized by him. Thus, syntheses of these systems will not be further discussed.

PYRAZOLES FUSED TO FIVE-MEMBERED HETEROCYCLES WITH ONE HETEROATOM

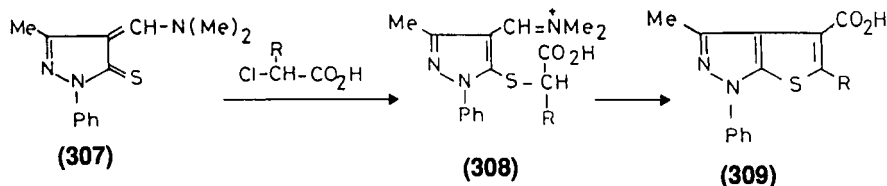
Three systems where pyrazoles are condensed to five-membered rings with one heteroatom exist (**300**–**302**). For pyrrolopyrazoles, a fourth isomer (**303**) is also possible. When the pyrazole ring is fused to a heterocyclic system in which the heteroatom is tetravalent, several isomeric structures can be drawn. Derivatives of **300**–**303** can be prepared either

**(300)****(301)****(302)****(303)**

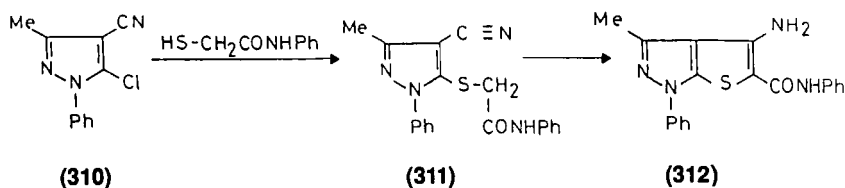
from pyrazole intermediates or from substituted monoheteroatomic five-membered rings. Thus, pyrrolo[2,3-*c*]pyrazoles are obtained by reacting 1-substituted aminopyrazoles with α -hydroxyketone and subsequently cyclizing the resulting pyrazol-5-ylaminoketones (72GEP2205136; 73JAP75593). For example, **304** gives **305** upon reaction with benzoin. The latter gives **306** upon treatment with phenyl phosphonic acid (PPA).

**(304)****(305)****(306)**

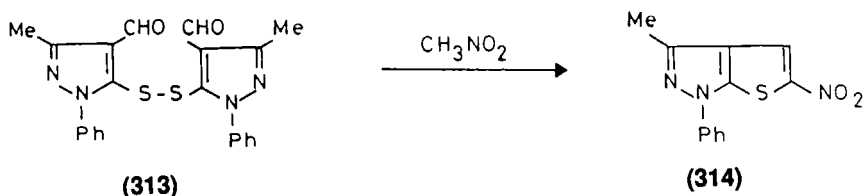
An essentially similar approach has been used for the synthesizing thieno[2,3-*c*]pyrazoles. Thus, **307** reacted with α -chloroacids ($R = H, Me$) to give the corresponding thieno[2,3-*c*]pyrazoles (**309**), via **308** (71ZOR1253).



Similarly 1-phenyl-3-methyl-4-formyl-5-chloropyrazole reacts with thioglycolic acid in the presence of alkali to yield a mercaptopyrazole derivative that could be cyclized to thieno[2,3-*c*]pyrazole in the presence of alkali (69KGS760, 69ZOR1498). Similar to this is the reported formation, via **311**, of **312** from **310** and mercaptoacetanilide (73ZOR2416).

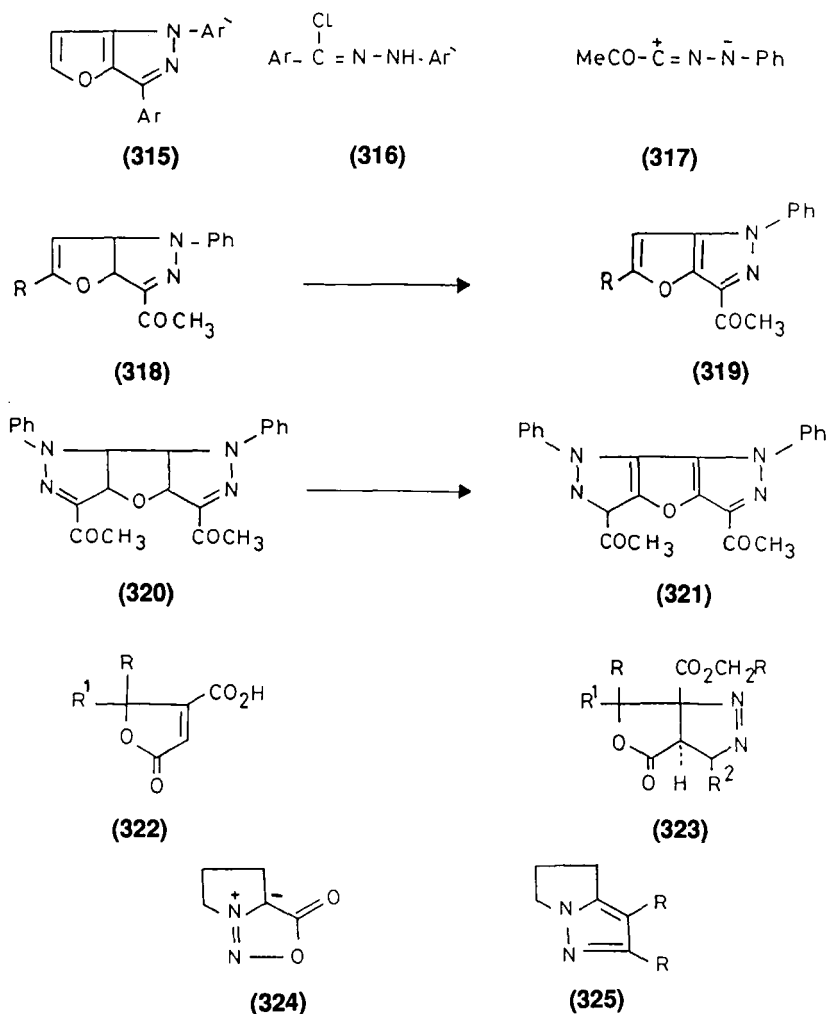


Conversion of ethyl 5-chloropyrazole-4-carboxylate into 4-hydroxythieno[2,3-*c*] pyrazoles, via ethyl 5-(phenylcarbomoylmethylthio)-4-pyrazole carboxylate intermediates, has also been reported (72USP3649641). The reaction of disulfide **313** with nitromethane gives **314** (74TL4069).

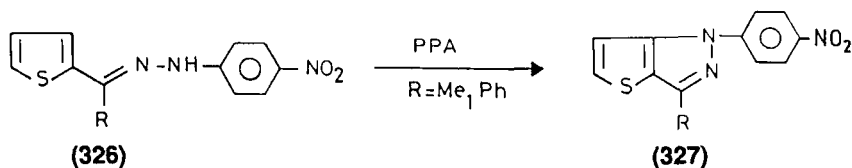


Furo[3,2-*c*]pyrazoles are produced via treatment of 4-allyl-3-methyl-1-phenylpyrazol-5-ones with bromine (84AKZ112). Caramella (68TL743) reported that **315** was isolated upon treatment of **316** with triethylamine in furan solution. It is assumed that the double bond in furan acts as a dipolarophile to the nitrile imine (generated by base treatment of **316**). The electrophilic carbon of the dipole attacks the α -position of the hetero ring, thus controlling the addition (70TL605). Similar addition of **317** to substituted furans gives **318**. Furan itself gives the bis adducts **320**. The structure of products was elucidated by spectral data as well as dehydrogenation to **319** and **321** (81CZ93). Similar work has also been reported by a French group (67BSF4179).

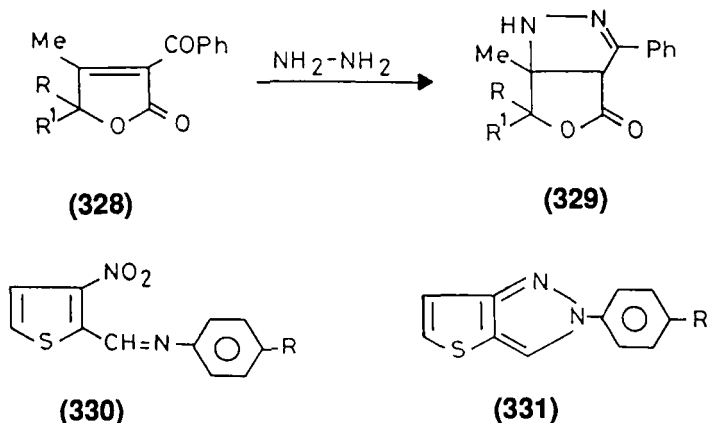
The reaction of maleic anhydride with nitrile imines also resulted in cycloaddition and formation of dihydrofuro[3,4-*c*]pyrazoles (83T129), and the reaction of **322** with diazoalkanes gives **323** (70BCJ2244). The addition of diazoalkanes to other 6-butenelides has been reported to yield furo[3,4-*c*]pyrazoles (74H601; 78MIP1; 83IZV2098; 84AKZ112), and cycloaddition of **324** with acetylene gives **325** (83TL1067) (Scheme 33). Thienopyrazoles are obtained via cyclization of 2-acyl and 2-aryolthiophene *p*-nitrophenylhydrazones, e.g., conversion of **326** into **327** (67CJC697).



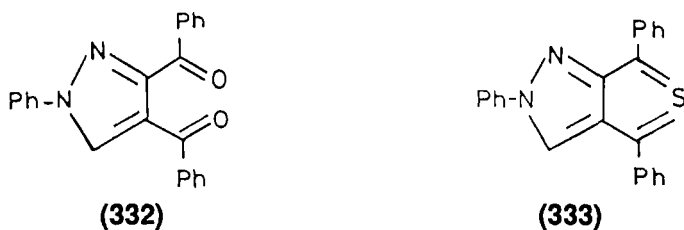
SCHEME 33



Similar synthetic approaches have been used to synthesize furo [3,4-*c*]pyrazoles, e.g., conversion of **328** to **329** (74AKZ954). Reductive cyclization of **330** gives **331**. Compound **330** is prepared by



condensing 2-methyl-3-nitrothiophene with *p*-nitrosodimethylaniline [79JCS(P1)1337]. Thieno[3,4-*c*]pyrazole (**333**) with tetravalent sulfur atom was prepared by reacting **332** with sulfur (74JA4276).

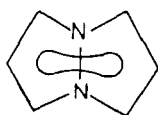


Simultaneous formation of a two-ring system from acyclic intermediates has also been reported. For example, the reaction of carbonyl-stabilized sulfur ylides with nitrile imines afforded furo[3,2-*c*]pyrazoles (69TL853).

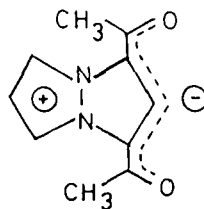
V. Chemical Properties

A. INTRODUCTION

The chemistry of pyrazoles condensed to six-membered rings can best be understood by assuming the system consists of a five-membered π -excessive heterocyclic ring that is fused to a six-membered π -deficient ring. Thus, electrophilic reagents are expected to attack either the pyrazole nitrogens or carbons. On the other hand, nucleophilic reagents are expected to attack the six-membered ring. Pyrazoles condensed to a five-membered ring with one heteroatom have a π -deficient pyrazole and an electron-rich, five-membered ring. In pyrazoloazoles, the pyrazole moiety is more electron-rich than the azole moiety; electrophiles thus attack this moiety. Only **334** can accurately be represented by a delocalized π -electron system. However, in substituted **334** (e.g. **335**) again, the system has an electron-rich moiety and an electron-deficient one.



(334)

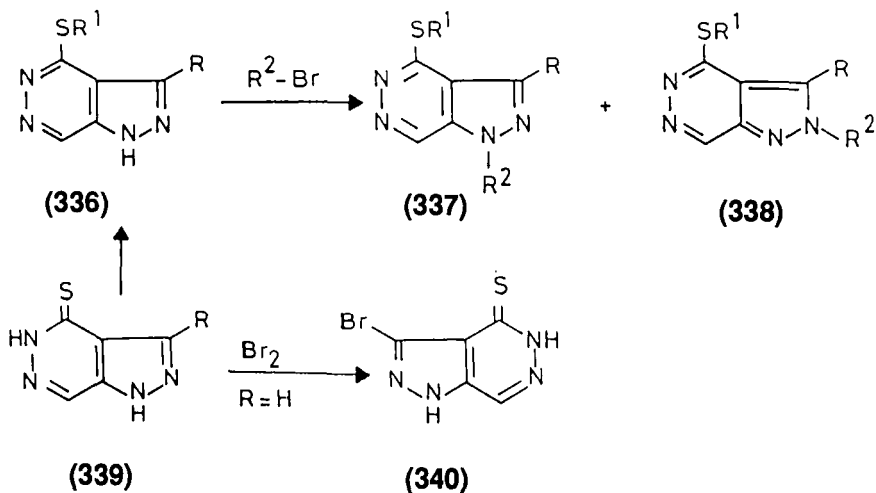


(335)

B. REACTIONS WITH ELECTROPHILIC REAGENTS

Only a few reports have dealt with the behavior of tetra-azaindenes toward electrophiles, and the reactions reported involved the pyrazole ring. Thus, alkylation of **336** with alkyl halides affords a mixture of the *N*-alkylated derivatives **337** and **338**. Compound **336** is produced by alkylation of **339**. Bromination of **339** ($R = H$) affords the 7-bromo derivative **340** (82JHC817) (Scheme 34). Nitration of 2-methylpyrazolo[3,4-*c*]pyridazine occurred at pyrazole C-3 (73JAP76893). Bromination of **341** with bromine in acetic acid gives **342** (83AP697).

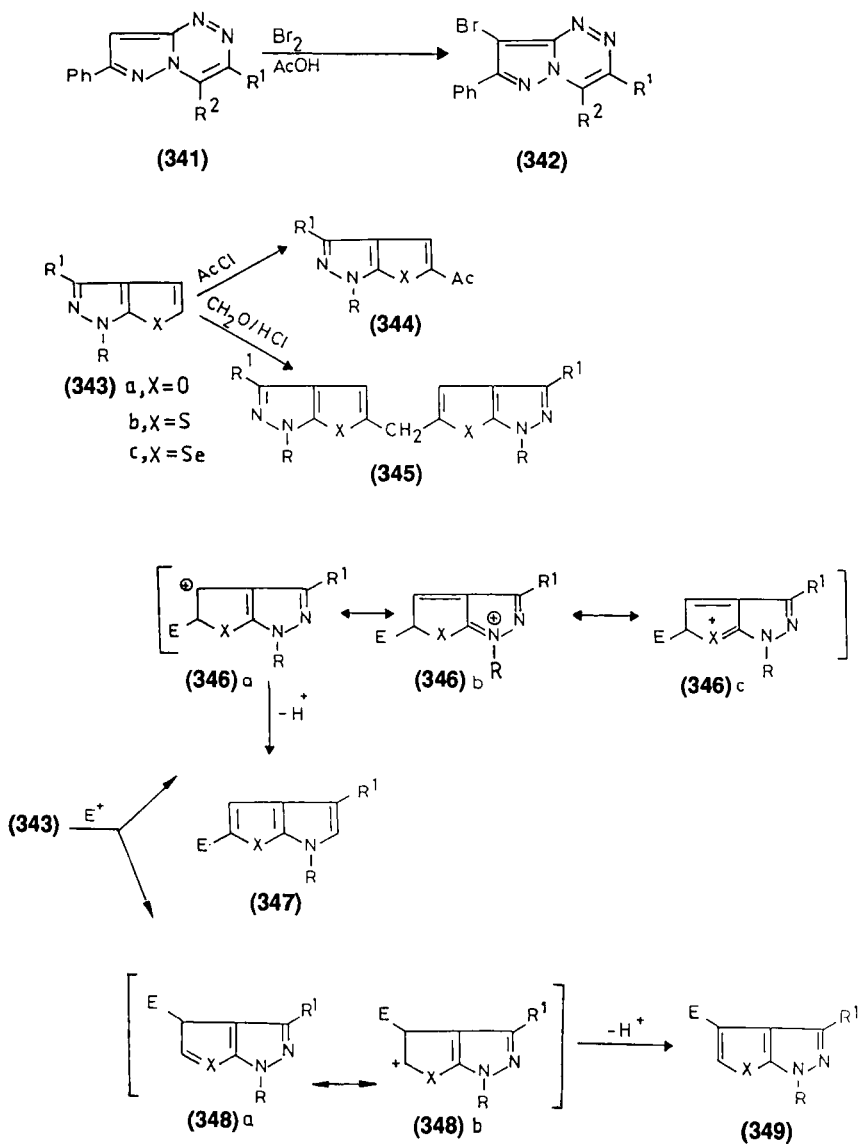
The furo[2,3-*c*]pyrazoles (**343a**) react with electrophilic reagents to yield 6-substituted derivatives. For example, **343a** ($R = Ph$; $R^1 = H$) affords the 5-acyl derivative **344a** upon treatment with acetyl chloride. Also **345a** is produced from the reaction of **343a** with formaldehyde in the presence of dry hydrogen chloride (69ZOR1498). This behavior simulates the reported



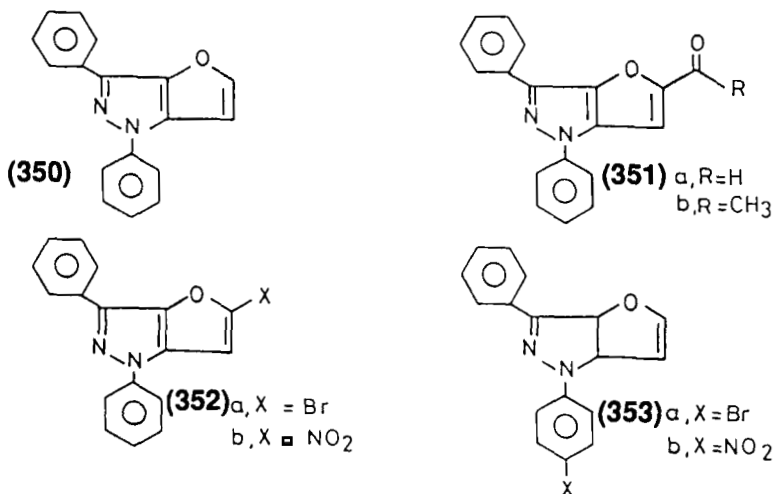
SCHEME 34

behavior or benzo[*b*]furans, where electrophilic substitution takes place at C-2. However, in contrast to the behavior of benzo[*b*]thiophene and benzo[*b*]selenophene, where substitution occurs at C-3, the treatment of **343b,c** with electrophiles also afforded 6-substituted derivatives. Thus, **344b,c** and **345b,c** are formed upon reacting **343b,c** with acyl halides and with formaldehyde in the presence of hydrogen chloride (72ZOR1750). It is argued that the resonance-stabilized reactive intermediates **346a–c** delocalize the positive charge on the pyrazole ring (cf. **346b**). This makes the ring more stable than the reactive intermediate **348a,b**, which is assumed to exist during the reaction and leads to substitution at C-4. Thus, the transition state leading to **349** will be thermodynamically favored, and, under kinetic control, predominate substitution at C-5 will occur (69ZOR1498; 73ZOR2201), leading to **347** and not **349** (73ZOR2201) (Scheme 35).

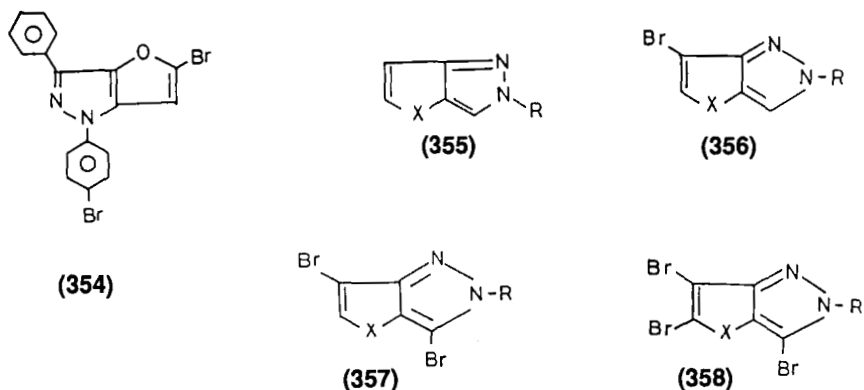
This is different from the situation in benzofused five-membered heterocycles with one heteroatom, where canonical forms delocalizing positive charge on the benzene moiety make a minimal contribution to the resonance hybrid of the intermediate. By analogous arguments, one expects isomeric **350** to react preferentially at C-5, as is experimentally found. Thus, formylation of **350** with phosphorus oxychloride in the presence of DMF gives the 5-formyl derivative **351a**. Acylation affords the 5-acyl derivative **351b**. Bromination of **350** with equimolecular amounts of bromine yields a mixture of **352a** and **353a**. Bromination with excess bromine



SCHEME 35



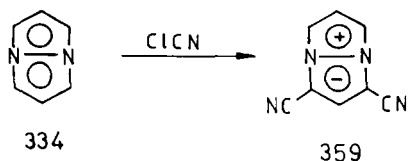
affords **354**. Nitration of **350** also involves both furan and aryl moieties, leading to a mixture of **352b** and **353b** (78YZ204). The reactivity of the *N*-phenyl function in **350** toward electrophilic reagents suggests that nitrogen lone-pair resonance extends to the phenyl ring.



Bromination of **355** affords a mixture of **356**, **357**, and **358** (77MI1). Bromination of 5-methyl-1,3-diphenylfuro[3,2-*c*]pyrazole with bromine gives the bromomethyl derivative (78YZ264).

Although **334** is very air sensitive, products of substitution by electrophiles are stable. Compounds **334** react with acylating agents to yield **335**, and with cyanogen chloride, **359** is produced. The observed direction of electrophilic substitution in **334** is consistent with charge distribution and

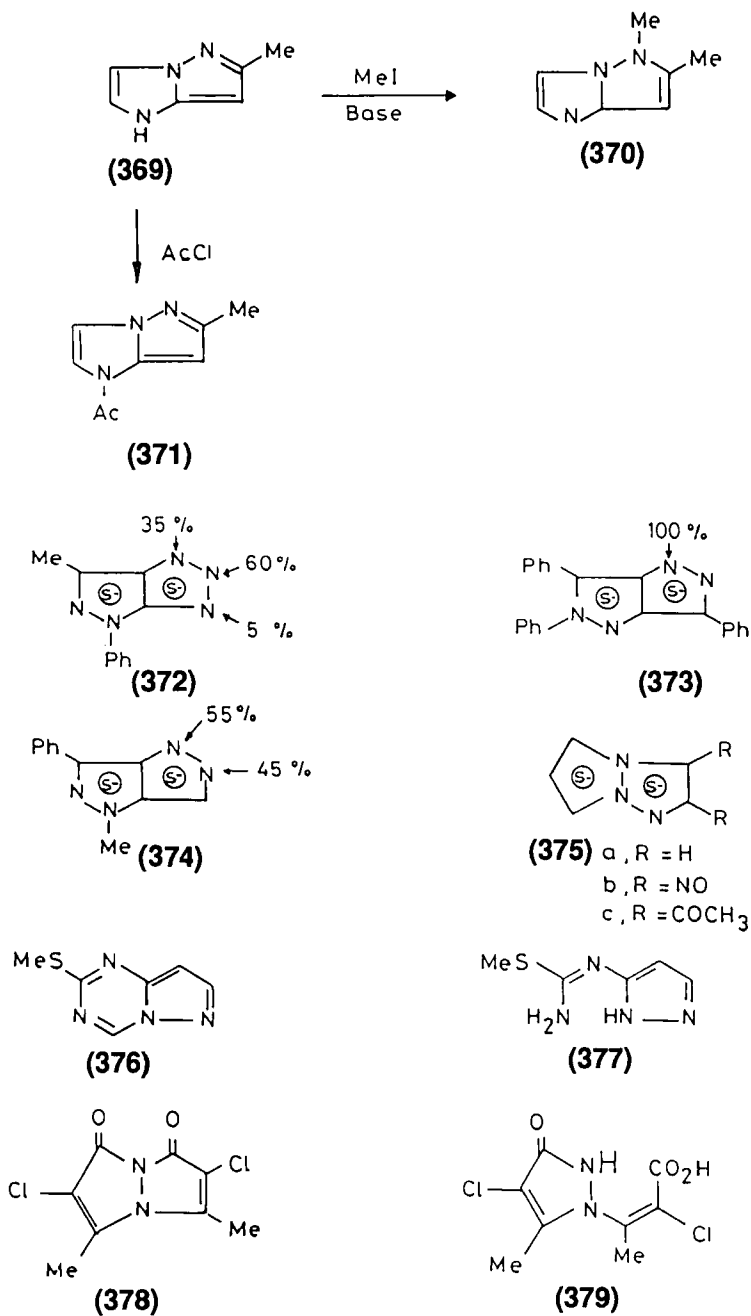
concentration of negative charge on the ring bearing the electron-withdrawing substituent (65JA4393).



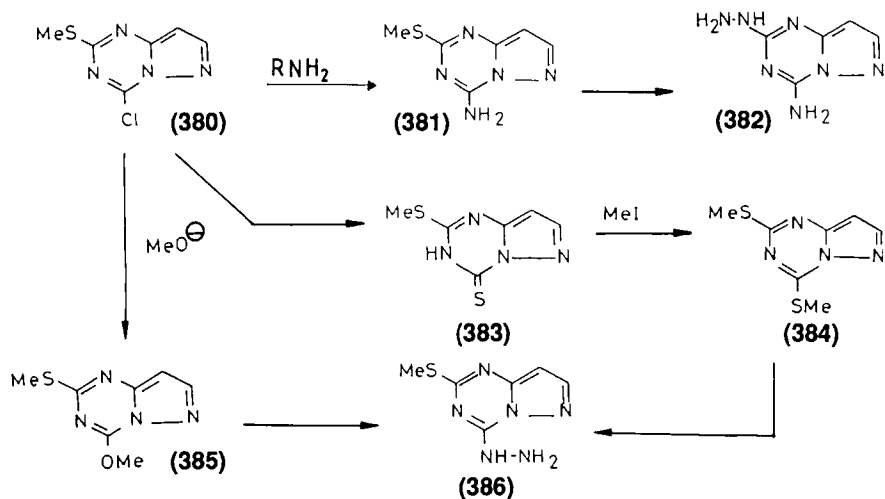
Depending on the substituent, two types of products may be isolated from reactions of **360** with bromine. When $R = H$, bromination affords the dibromo derivative **361** in a yield higher than that obtained from treatment of the 4,4-dibromo-3-methylpyrazolone with base. In the latter case, the trace isomer is also produced. When **360** ($R = Me$) is treated with bromine, the monobromo (**362**) or dibromo (**363**) derivatives are formed (80JA4983; 81JOC1666, 81JOC1673). Compound **363** was converted into **365** upon reaction with amines. Treatment of **363** with sodium sulfide gives **364** (81JOC1666, 81JOC1673). The behavior of **360** on bromination is also dependent on the substituent. Thus **360** ($R = CH_2-Br$ or Ph) gives only a monobromo derivative (80JA4983; 86JA4527).

Pyrazolo[4,3-*c*]pyrazoles such as **366** couple with aromatic diazonium salts to yield the corresponding arylazo derivatives **367** (74TL23; 78AHC183). The behavior toward electrophiles of pyrazoles fused to five-membered heterocycles with more than one heteroatom has been extensively investigated, but it has also been previously surveyed (78AHC183); here we give only a brief discussion. Generally derivatives of type **368a-c** react with electrophiles at the pyrazole C-3, which is sufficiently electron-rich to couple with aryldiazonium salts (78AHC183). Bromination and nitrosation of this site have also been observed. Derivatives of **368a-c** also condense with aromatic aldehydes to yield alkylidene derivatives, which have been extensively used as photosensitizers (Scheme 36).

Acylation and alkylation usually involve ring nitrogen and, in many cases, mixtures of products are obtained (Scheme 37). Conditions usually used in electrophilic substitution on aromatic systems are employed to effect substitution at ring carbons. *N*-Alkylation is usually carried out on the sodium or silver salts of the azoles (70BCJ3587). Examples shown are the conversion of **369** into **370** upon treatment with methyl iodide in the presence of base and the preparation of **371** from **369** and acetyl chloride. Product compositions of the *N*-methylations of **372-374** are also shown. The mesoionic derivative **375a** is nitrosated at C-3 to yield **375b**. Acylation also involved the same site to give **375c** (78TL1291).



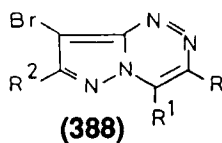
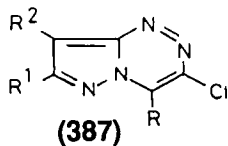
SCHEME 37

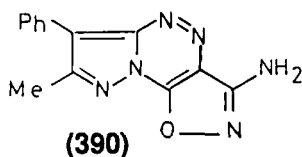
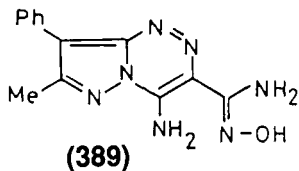


SCHEME 38

Displacement of halogen substituents by nucleophiles, both on the pyrazole ring and on the ring fused to the pyrazole, has been reported and constitutes a main route for preparing substituted azindenes. Thus, upon treatment with amines, 4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,2,3,5-tetrazine (**380**) was converted into the amine **381**, which gives the hydrazino derivative **382** upon treatment with hydrazine. Compound **386** is also obtained by reacting **384** or **385** with hydrazine. Compound **384** is formed by reacting **380** with sodium sulfide and methylating the resulting compound **383**. Compound **385** is prepared from **380** and methoxide ion (74JHC199) (Scheme 38).

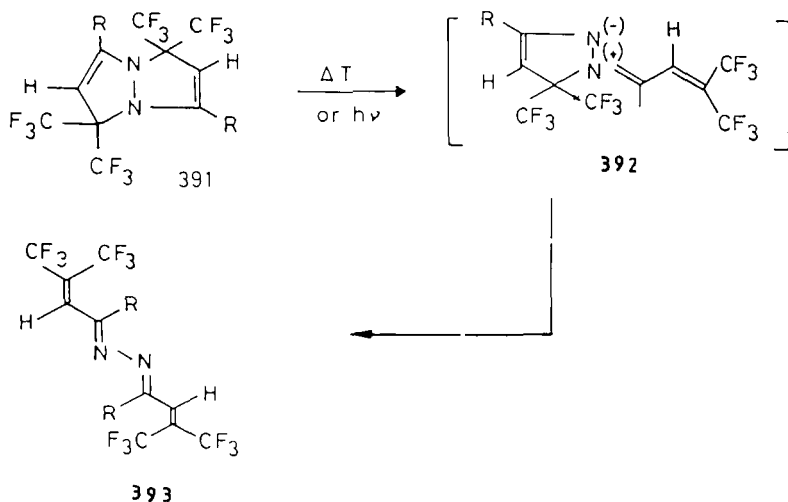
Substitution of the halogen in **387** and **388** by nucleophiles has also been reported (81M245; 83AP697), as has the cyclization of **389** into **390** (83G219). Ethyl 1,5-diaryl-3-trifluoromethyl-4-oxopyrazolo[3,4-*d*]pyridazin-7-ylacetate afforded bicyclic 5(5-oxopyrazol-3-yl)pyrazolines upon treatment with ethanolic sodium ethoxide (88JHC134).



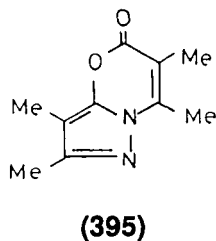
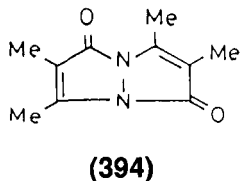


D. PERICYCLIC REACTIONS

Diazabicyclo[3,3,0]octa-2,6-dienes of type **391** undergo a sequence of electrocyclic reactions upon thermolysis and photolysis (82JPC338) to yield 4,5-diazaocta-1,3,5,7-tetraenes (**393**), probably via **392** (79CB2620). The influence of the substitution pattern on the conditions necessary for initiation of the reaction and on the valence isomeric equilibria have been studied (86JPC5552).



The antibimane **394** rearranged quantitatively to lactone **395** upon irradiation at 320 nm. Symmetrical bimanes give one lactone, whereas unsym-

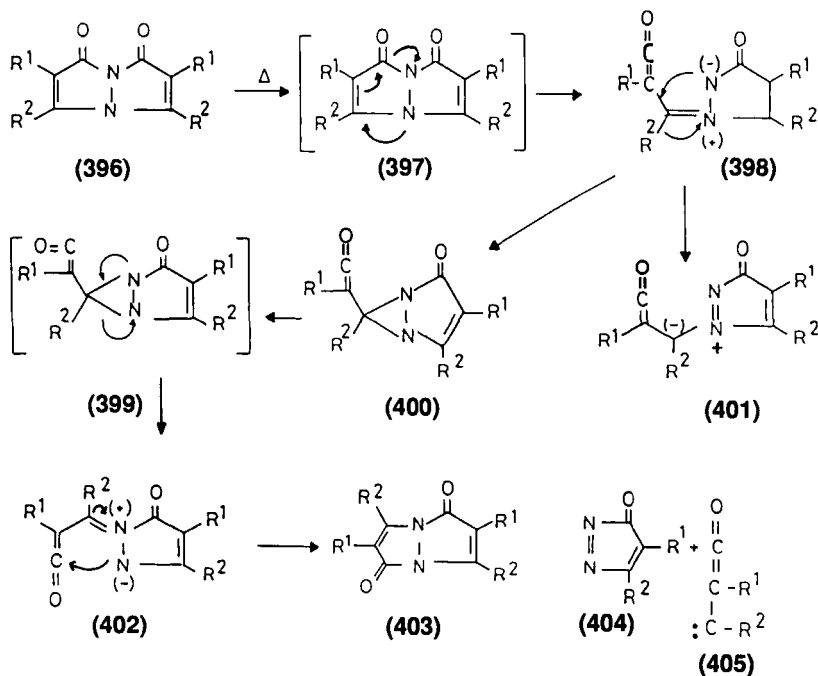


metrical analogues give two. The quantum yield of lactone is often high and depends on biman substitution and solvent viscosity. Fast, inter-system-crossing oxygen inhibition of lactone formation, and efficient formation of lactone via a triple sensitizer, implicate the triplet state as a key intermediate. The suggested mechanism of lactone formation involves a twisted $\pi-\pi^*$ triplet (82JOC207; 84CPB930).

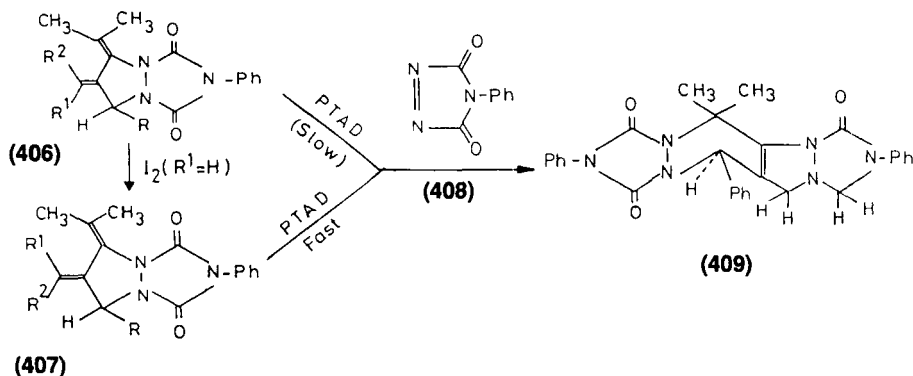
The formation of 9,10-dioxo-*anti*-bimanes (403) upon thermolysis of 9,10-dioxo-*syn*-bimanes (396) is thought to occur with intermediates 397–402 and 404–405 by the mechanism demonstrated in Scheme 39 (80JA4983).

Both 406 and 407 ($R = H$) react with PTAD (408) to yield the same 1 : 1 adduct 409. Apparently the conformation of 406 and 407 are substantially different such that PTAD approaches opposite sides of the diene system in the molecule, thus affording the same compound (73JA1553) (Scheme 40).

The rate of reactions of these alkylidene derivatives was found to be sensitive to the nature of the alkylidene substituent and to the stereochemistry around the 7-alkylidene double bond. Thus, 7-isopropenyliden derivatives [406 and 407 ($R^1 = CH_3$)] do not react (73JA1553).



SCHEME 39



SCHEME 40

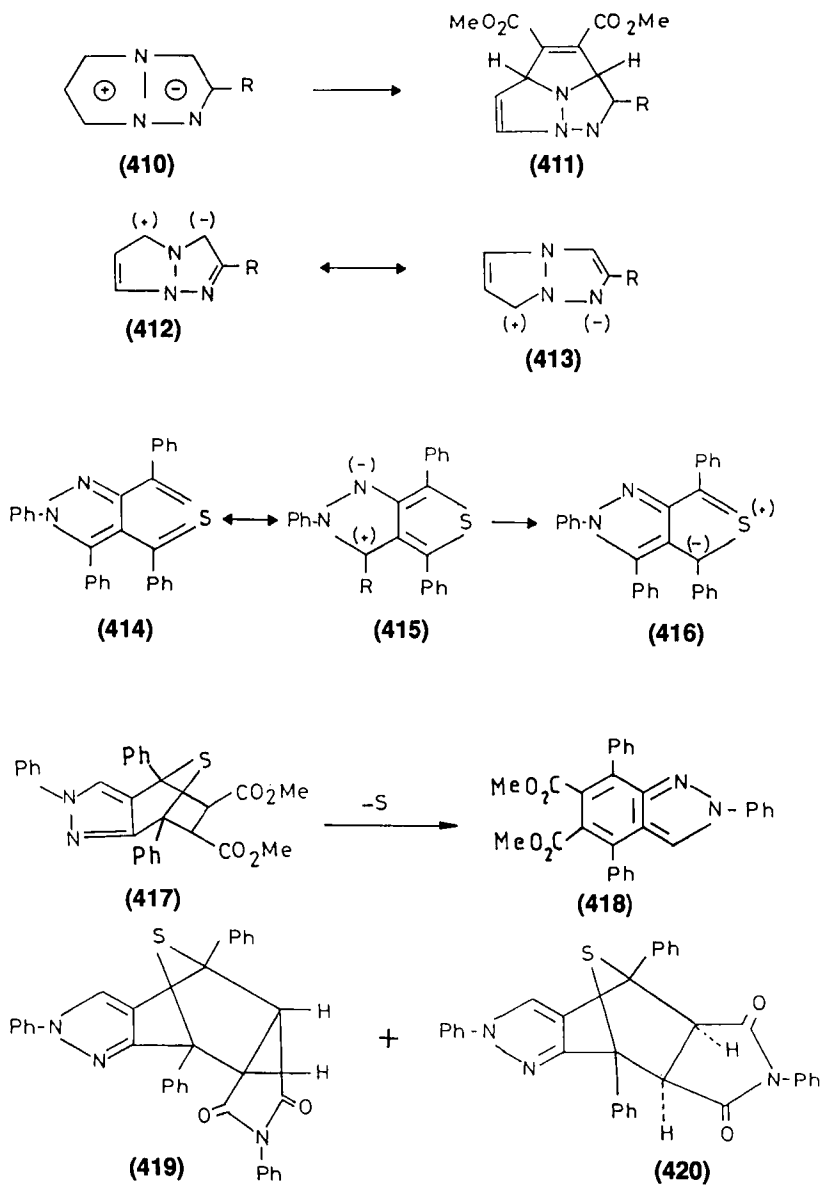
The reaction of **410** with dimethyl acetylenedicarboxylate yields **411** (78TL1291). Since **410** can be represented as the azomethine ylide **412** or the azomethine-imine ylide **413**, this result may indicate that the azomethine ylide is more reactive in cycloadditions with acetylenes than azomethine-imine ylides.

2,4,6-Triphenylthieno[3,4-*c*]pyrazole (**414**) can be presented as a hybrid of dipolar-contributing azomethine imine ylide (**415**) or thiocarbonyl ylide canonical forms **416**. Upon reacting this ylide with electron-poor olefins, it behaved like a thiocarbonyl ylide. Thus, with maleimide, a mixture of endo (**419**) and exo adducts (**420**) were obtained (74JA4276), which resulted from addition at the thiocarbonyl moiety. The reaction of **414** with dimethyl acetylenedicarboxylate gives the desulfurized indazole **418** in addition to the adduct **417** (Scheme 41).

VI. Physicochemical Studies

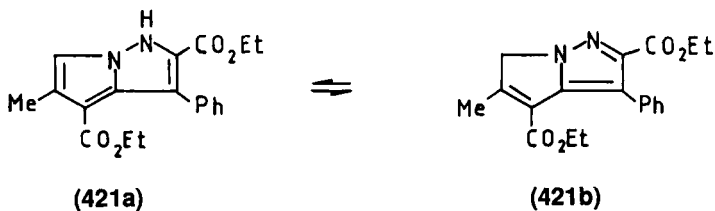
A. ANNULAR TAUTOMERISM

The exchange of protons constituting part of a heterocyclic system is called annular tautomerism. While this type of tautomerism has not been closely examined in pyrazoles fused to any six-membered ring, it has been investigated in depth for pyrazoles fused to five-membered rings. The position of equilibrium between different tautomers depends a great deal on the nature of substituents on the ring. However, there are rules that may enable prediction of predominance of one form or other forms. Thus, according to Elguero *et al.* (78AHC183)

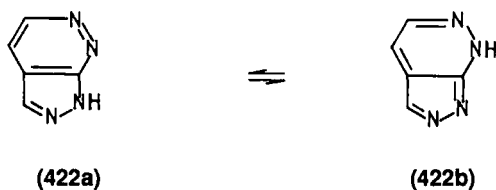


SCHEME 41

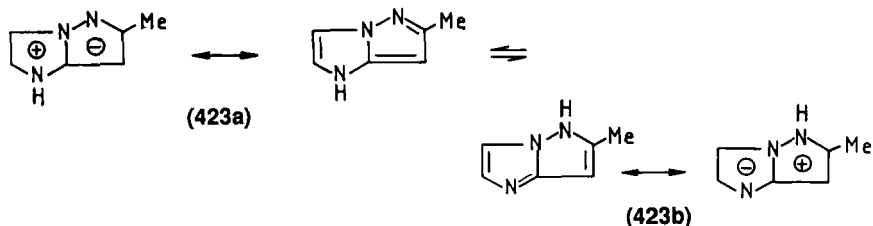
(i) Only one heteroatom of two adjacent ones can contribute a lone pair to constitute a 10 π -electron system. Thus, **421a** exists mainly as **421b**.



(ii) Benzenoid systems are more stable than quinonoid ones. Thus, **422a** is more stable than **422b**.

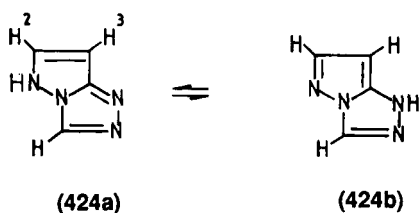


(iii) The five-membered ring that carries the tautomeric hydrogen will be π -electron deficient; the other ring will be π -excessive (e.g. **423**). Thus, the tautomer that carries the positive charge in the more "basic" ring and the negative charge in the more "acidic" ring will be the most stable. Since basicity increases and acidity decreases along the series tetrazole, ν -triazole, s -triazole, pyrazole, imidazole, and tautomer **423a** should be more stable than **423b** (74T2744). This agrees with experiment results. The

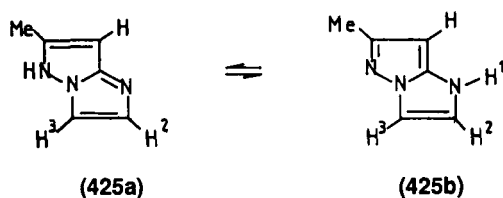


$^1\text{H-NMR}$ spectrum in dimethylsulfoxide (DMSO) of **424** (70CB3284) shows $J(2\text{H}3\text{H}) = 2.3$ Hz. By analogy with other coupling constants in pyrazoles, this has been taken as an indication for coupling across a double bond, which indicates that **424a** predominates. This conclusion appears unlikely; **424a** can be considered an aromatic 10 π -electron system only if lone pairs on two adjacent nitrogen atoms did participate in resonance.

This contradicts rules (i). However, in dioxan, an investigation based on dipole moment measurements concluded the predominance of **424b**. In



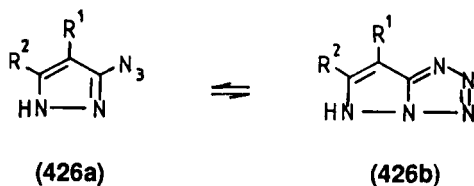
425, $^1\text{H-NMR}$ indicated that **425b** predominated as coupling of H^1 and H^2 was observed (73JHC411).



Theoretical calculations (73TL2703) of tautomeric equilibria in these systems agree with experiment results. These calculations are based on comparing experimental with theoretical UV.

B. RING-CHAIN TAUTOMERISM

Several investigations of the ring chain tautomerism in **426a** \rightleftharpoons **426b** were reported. The position of the equilibrium in this system has been investigated by Claramunt *et al.* (77MI1). First-order kinetics have been determined by IR and $^1\text{H-NMR}$ in sodium ethoxide solution. The reaction rate of cyclization of **426a** into **426b** depends upon both substituents on the



pyrazole ring (83MI2). The effect of the substituent at C-4 of pyrazole follows a Taft relationship $\log(k/k_0) = 2.0 \sigma_1 + 3.2 \sigma_R$.

C. TAUTOMERISM OF FUNCTIONAL SUBSTITUENTS

This subject has not yet received attention. However published IR and ^1H -NMR results (76JHC1305; 79JOC4547) indicate that, while amino substituents exist as such, the hydroxy substituents exist predominantly in the oxo form (78JHC813; 84JPR811, 84KGS697). Thiol exists in thione form (79JOC4547).

D. SPECTRAL STUDIES

Reported ^1H -NMR data for pyrazoles linked to six-membered heterocycles indicate that the protons on the six-membered ring are more deshielded than protons on the five-membered ring. The most deshielded protons are those situated in positions that permit interaction with the heteroatom. Thus, in pyrazolo[1,5-*b*]pyridazines, H-4 appeared at δ 8.36–8.44 depending on the nature of the substituents (74CPB1814). The ratio of

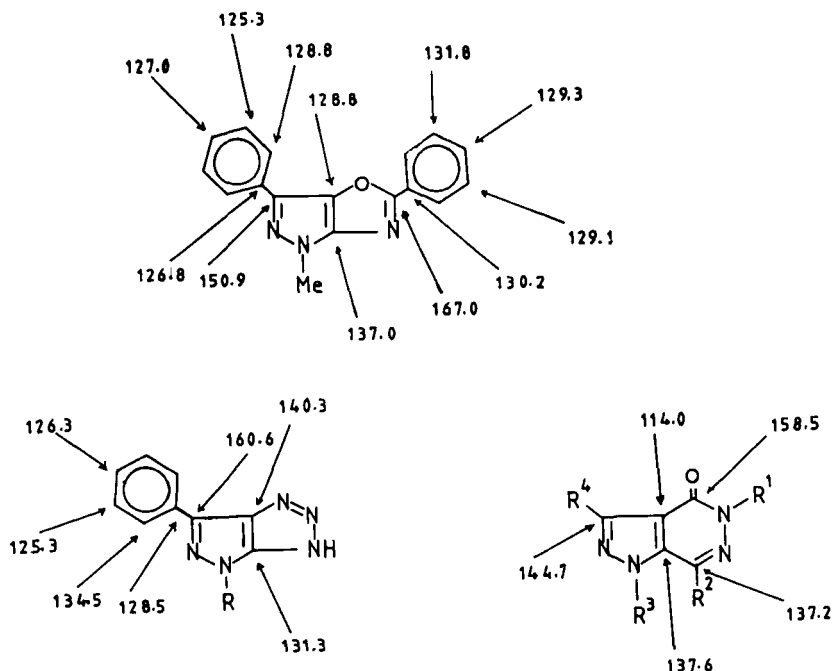


FIG. 1

FIG. 2

tetrazole (**427**) was determined by x-ray diffraction (Fig. 2). The compound crystallizes in space group $P2_1/a$ with four molecules in a unit cell of dimensions $a = 10.184$, $b = 28.827$, $c = 4.090$ Å; $B = 123.37^\circ$. The data shows that the pyrazole ring is more aromatic than the tetrazole, which has an N_2-N_3 bond shorter than all the other N—N bonds. In the pyrazole, all bonds (N—C or C—C) have approximately the same length. In the crystal, molecules are stacked along the c direction with a mean interplanar spacing of 3.40 Å. There is essentially no overlap of the five-membered rings in adjacent layers; N(3) and N(4) of one molecule lie nearly over C(7a) and C(7), respectively, of the adjacent molecule. Intermolecular contacts with a layer correspond to the van der Waals interactions (78JHC395).

F. ULTRAVIOLET INVESTIGATIONS

A variety of investigations using x-ray analysis of the structure of pyrazolo[1,2-*a*]pyrazolium salts have been reported. [75CSC317; 81CC348; 82LA845]. These investigations show that this ring system constitutes a $4n\pi$ -mesoionic, heterocyclic, antiaromatic system [80ZN(B)1002].

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Thianthrenes

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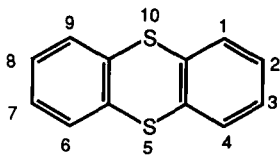
I. Introduction

The chemistry of thianthrenes was briefly (51M11), then comprehensively reviewed (up to 1960) (66HC1155); a review lecture dealt with some electron-transfer reactions of the thianthrene radical ion(1+) (85PS111). Chapters on the "Electrochemistry of the Sulfonium Group" (81M16) and "Organosulfur Cation Radicals" (81M11) in the Patai series', "The Chemistry of the Sulfonium Group," include discussions of thianthrene chemistry.

Thianthrenes have not been dealt with previously in *Advances in Heterocyclic Chemistry*. This chapter covers the chemistry of thianthrenes from 1960 to the end of *Chemical Abstracts*' 1988 coverage. Earlier references are included only where they are of particular significance or serve to place later work in context. The family of linear tri-6-membered-cyclic heterocycles with group VIb elements located 1,4- in the central ring, of which thianthrene is a member, have been referred to as dibenzodichalcogenins, chalcogenanthrenes, and chalcanthrenes. This review will not attempt to draw comparisons between the chemistry of thianthrene and that of the other chalcanthrenes.

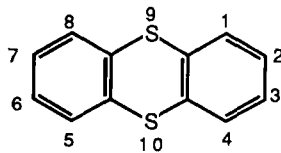
Thianthrene is numbered as shown in **1** using current *Chemical Abstracts*' numbering; before 1937, the numbering shown in **2** was used in *Chemical Abstracts*. The ring positions ortho to sulfur have been termed α , and the others are termed β . Alternative names for thianthrene, found more in older literature, are dibenzo- 1,4-dithiadine, dibenzo- 1,4-dithiin, di-*o*-phenylene sulfide, and diphenylene disulfide. The literature also contains references to *o*-thianthrene; this is dibenzo[*c,e*][1,2]dithiin, (**3**).

Species **4**, produced from thianthrene by loss of an electron from a sulfur, is correctly known as thianthrene radical ion(1+); most authors have referred to it as the thianthrene radical cation or the thianthrene cation radical. The species produced by loss of two electrons from the central ring, and for which **5** is probably a resonance contributor, is termed thianthrenediium. Sulfonium salts (**6**) produced formally by utilizing a sulfur lone-pair in bonding to R^+ , are 5-*R*-thianthrenium salts. Thianthrene sulfoxides and sulfones are named as oxides, e.g., thianthrene-5,5,10-trioxide (**7**). The early literature, dating from before the relative stereochemistry of the two thianthrene 5,10-dioxides had been established, refers to the *cis*-isomer as the α -isomer and the *trans*- as the β -isomer.



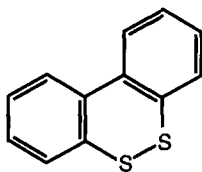
(1)

Current numbering

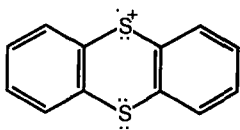


(2)

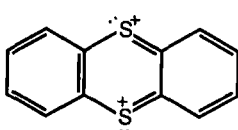
Numbering before 1937.



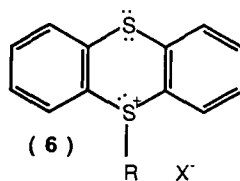
(3)



(4)

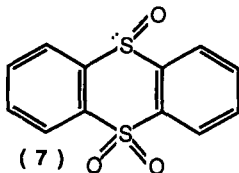


(5)



(6)

In kinetic expressions, acronyms which have been used in the literature for thianthrene include T, Th, Ta, TA, TH, and Thia. On the grounds that T is not an element symbol and Thia is too long, this review will use T for thianthrene, therefore T^+ is used for the thianthrene radical ion(1+), and T^{2+} is used for thianthrenediium.



(7)

II. Structure and Physical Properties

A. CRYSTALLOGRAPHY, DIPOLE MOMENTS, AND OTHER MEASUREMENTS AND CALCULATIONS RELEVANT TO MOLECULAR STRUCTURE

Emerging first from measurements (66HC1155) that showed thianthrene to have a dipole moment in the range 1.45–1.57 D, it has been long

established that thianthrene is not flat. Its shape may be visualized as that of a folded piece of paper, or more lyrically as a butterfly in which the fold line passes through the two sulfurs, and each wing is essentially planar and the central ring is a boat.

Precisely, the molecule has a folded C_{2v} configuration, the fold angle being the dihedral angle between the two planes defined by the two aromatic rings and attached sulfur atoms. A value of 128° for the fold angle of thianthrene in the solid state was obtained by X-ray crystallography (66HC1155). The folded conformation allowed the C-S-C angles to be normal and the sulfur atoms essentially tetrahedral. A redetermination [84AX(C)103] at room temperature and measurement at 163 K gave values of 128.1° and 127.1° , respectively, for the fold angle, a value of 1.771 \AA for the C-S bond length at both temperatures, and 100.2° and 100.1° for the C-S-C angle at room temperature and 163 K, respectively. In the crystalline solid state, there is a close contact, 3.78 \AA , between a sulfur of a molecule in one unit cell and a sulfur of a molecule in an adjacent cell (79JCP305).

As illustrated in Fig. 1A, individual molecules of thianthrene [and also 2,3,7,8-bis(methylenedioxy)thianthrene] stack in the same manner as roofing tiles [82JCR(M)3501, 82JCR(S)334], whereas in crystals of 2,3,7,8-tetramethoxythianthrene, the asymmetric unit contains three molecules (Fig. 1B), two are stacked above each other, but the third lies perpendicular to this pair. In this last case, the asymmetric units are arranged so that no more extensive stacking than this occurs.

The fold angle is relatively insensitive to structural variation and substitution, particularly by polar substituents, which causes some flattening of the fold: crystallographic determinations found 131.1° [71AX(B)1523] and 130.2° (82CSC681) for 2,7-dimethylthianthrene; 132.0° (80CSC909) for perfluorothianthrene; 131° for 2,3,7,8-tetramethoxythianthrene [82JCR(M)3501; 82JCR(S)334], 137° (77JOC2896; 78CSC745) for 1,6-dinitro-3,8-bis(trifluoromethyl)thianthrene; and 135.7° (82JHC833) for thianthrenium bisethoxycarbonylmethylide. In this last molecule, as shown in **8**, which exaggerates the fold angle for illustrative purposes, the sulfur

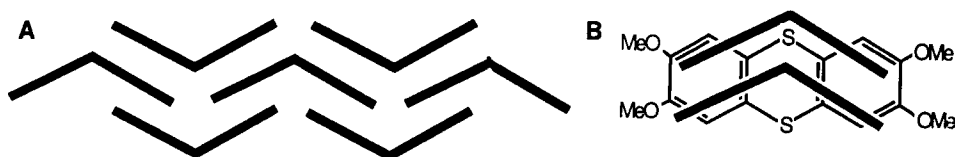
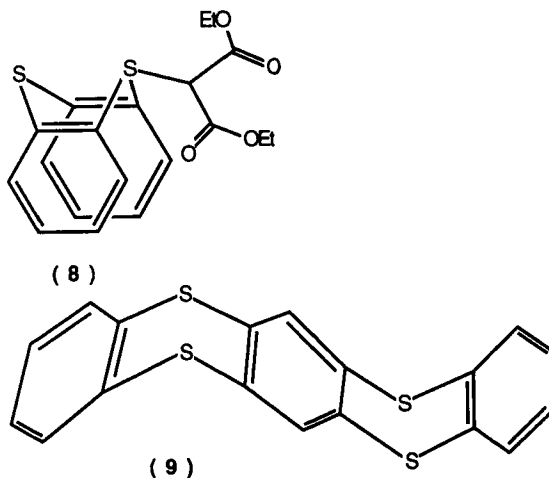


FIG. 1. A, Individual molecules of thianthrene stacked in the same manner as roofing tiles; B, two molecules stacked above each other, with a third lying perpendicular.



substituent is located equatorially with respect to the central-ring boat, and the plane of the ylid unit is essentially perpendicular to a plane defined by the four carbons of the central ring. The fold angles in the two boats of the overall chair conformation of 5,7,12,14-tetrathiapentacene (9) are each 131.5° [86AX(C)720]. Even coordination to a metal via a sulfur, as in thianthrenegold(III) chloride (chloroform solvate), or via a benzene ring, as in η^6 -2-methylthianthrene(η^5 -cyclopentadienyl)iron(III) hexafluorophosphate, has little distorting influence on the fold angle. Values of 129.5° [78AX(B)3364] and 127.4° (85JOM387), respectively, were given by crystal structure determinations.

In the charge-transfer complexes between 2,3,7,8-tetramethoxythianthrene and 7,7,8,8-tetracyanoquinodimethane [77IZV208, 77ZSK898; 82JCR(M)3540, 82JCR(S)336], and hexachlorodibenzo-*p*-dioxin-2,3-dione [86ZN(B)1133], values of 137.9° and 137.8° , respectively, were found. These complexes are of a typical charge-transfer type that have stacks of alternating donor and acceptor molecules, the process of stacking in the crystal presumably being at least partially responsible for the 10° flattening of the thianthrene moiety. Similar flattening (140.6°) was found in the charge-transfer complex of dinaphtho[1,2-*b*:1',2'-*e*]-1,4-dithiin with tetracyanoquinodimethane (TCNQ) [88JCS(P2)427].

The folded nature thus demonstrated experimentally is consistent with the conclusion (63T471; 64JA164) from molecular orbital (MO) calculations that, in thianthrene, there is little overlap between a sulfur lone pair and the two *p* orbitals adjacent to it (78PS1). Similarly, later calculations showed that the resonance energy of thianthrene is essentially that of the two benzene rings (80T2711).

Although there is no report of an X-ray structural study of a 5-R-thianthrenium salt, crystal structures have been determined for three of the S-oxides of thianthrene: the fold angle is 123° for *cis*-thianthrene 5,10-dioxide (63AX310), 127.7° for *trans*-thianthrene 5,10-dioxide [63AX310, revised in 66AX21, recalculated in 70AX(B)451 and 84AX(C)103], and was found to be 127° for thianthrene 5,5,10,10-tetroxide (63AX310). But, a later determination of the tetroxide at 163 K found two crystallographically distinct molecules with fold angles of 138.0° and 144.0° in the unit cell [84AX(C)1378].

It is of considerable interest to compare values of fold angles, determined by the X-ray method on the crystalline state, with those produced by different measurements in solid and other phases. For example, electron diffraction-analysis [75JCS(F2)1173] and photoelectron spectroscopic studies [81ZOB1293; 83JCS(P2)1109, 83ZOB2537] of thianthrene gave rather wide-ranging values of 131.4° , and 110° , 116° , and 142° , respectively. Solution measurements give somewhat larger values than those typical for the crystalline state. Perhaps this is not surprising, and no doubt reflects, in part, solute-solvent interactions. Thus, later dipole moment values of 1.45 D, leading to a calculated fold angle of 140° (71MI2) for thianthrene in a polymer matrix, were determined. In benzene solution, 1.51 D (64BSF2119), 1.41 D (144° fold angle) (65JCS571), 1.37 D (73BCJ3359), and 1.50 D (142.4° fold angle) [83JCS(P2)1109] were determined. Kerr-constant measurements led to 140° (65JCS571), a study of thianthrene by molecular optical anisotropy produced a value of 142° (79MI2), and finally, NMR measurements gave values of 140.2° and 141.6° (in different liquid crystal solvents) (83JA125), and 140.6° (139.8° for 2,7-dichlorothianthrene) [82JCS(P2)1209] for the fold angle.

Dipole moment measurements of solutions of *cis*- (64BSF2119; 65JCS571) and *trans*-thianthrene 5,10-dioxide (65JCS571) and of thianthrene 5,5,10,10-tetroxide (65JCS571) gave values of 1.86 and 1.70, 4.88, and 5.11 D, from which fold angles of 139° , 130° , and 140° respectively, were calculated.

The somewhat larger estimates of fold angles obtained other than in the solid phase may reflect both solvent effects and a lower barrier to flapping. However, it seems misleading to describe thianthrene, as was done on the basis of modified neglect of differential overlap (MINDO) calculations, as an "inherently" planar molecule (86H2757). That a molecule of thianthrene flaps like a butterfly when in solution (65JCS571) or gaseous phase is made clear by various estimates for the energy barrier to such inversion: 6–7 kcal mol⁻¹, from early LCAO*-calculations (63T471); 4.6 kcal mol⁻¹,

* LCAO, Linear combination of atomic orbitals.

from molecular mechanics calculations (85JA5323) (which also gave estimated values of 1.74 D and 130° for dipole moment and fold angle); ≥ 4 kcal mol $^{-1}$, from the electron diffraction study [75JCS(F2)1173]; and 3.6 kcal mol $^{-1}$, from dielectric measurements (71MI2) in a polystyrene matrix. From NMR studies on thianthrene and its two 5,10-dioxides (showing no line broadening) inversion is rapid down to -40°C , and for *cis*-thianthrene 5,10-dioxide, the barrier was estimated as ≥ 1 kcal mol $^{-1}$ (67JA1579). It seems that conclusions (64SA159) drawn from dielectric-relaxation time measurements regarding the rigidity of the fold in a thianthrene molecule (65JCP473) and, earlier, of molecules of 2,7-dimethylthianthrene (58JPC772) should be set aside.

The intriguing question regarding the fold angle in the thianthrene radical ion(1+) (4) has not been settled experimentally; however, in two crystalline salts of 2,3,7,8-tetramethoxythianthrene radical ion(1+), the tricyclic heterocyclic nucleus is *planar*. One may see, however, from resonance contributors, such as those shown in Fig. 2, that the delocalization and hence planarity would be encouraged by mesomeric participation by the ring substituents in the substituted case. Indeed, X-ray crystallographic analyses of the SbCl_6^- and I_3^- salts showed shortened C—O bond lengths as well as shortened C—S bond lengths, as implied in Fig. 2. In each salt, cations and anions are aligned in segregated stacks. In the SbCl_6^- salt, the radical cations align as shown in Fig. 3, and in the I_3^- salt, dimers are arranged (Fig. 4) in a stairlike manner [87ZN(B)169].

B. ^1H -NMR SPECTROSCOPY

The chemical shift, δ , for H-1 in thianthrene in CDCl_3 is 7.48, and the shift for H-2 is 7.23. Coupling constants are $J_{12} = 7.9$, $J_{13} = 1.3$, $J_{14} = 0.3$, and $J_{23} = 7.4$ Hz (66CJC1211; 74OMR1115). Downfield shifts of 29.7 Hz and 20.5 Hz for H-1 and H-2 signals (respectively), in the presence of silver nitrate, were taken as evidence for complexation at sulfur (70OMR491). Measurement in the presence of $\text{Eu}(\text{fod})_3$ allowed the detection of a trace of dimethyl thianthrene-2,8-dicarboxylate 10-oxide in the presence of its 2,7-isomer (77TL2643).

In 1,1,2,2-tetrachlorethane solution, the spectra of thianthrene and *trans*-thianthrene 5,10-dioxide are temperature independent; for the *cis*-isomer, the lower-field resonance shifts further downfield with increasing temperature while the signals for 2-, 3-, 7-, and 8- protons remain constant over a 200° range. In chloroform, small, apparant temperature-dependent shifts for thianthrene, at all positions, were attributed to temperature-dependent shifts of the reference solvent signal. Using this, it was shown

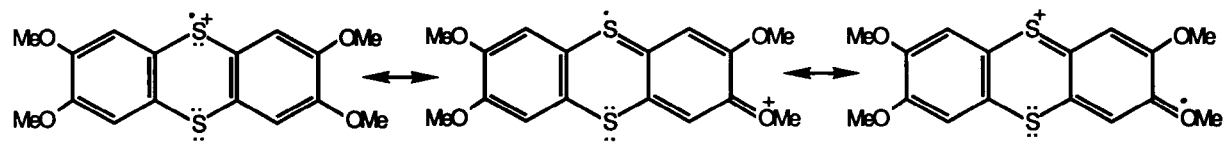


FIG. 2. Shortened C—O and C—S bond lengths in SbCl_6^- and I_3^- salts observed by X-ray crystallography rationalized by resonance contributions.

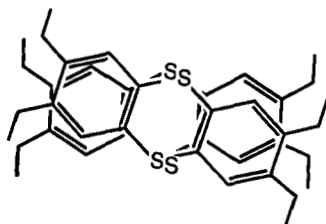


FIG. 3. Alignment of the radical cations in the SbCl_6^- salt. (Viewed along stack, eclipsed units not shown.)

that the temperature dependence of the low-field signal of the *cis*-dioxide was comparable in chloroform to tetrachloroethane. This dependence was rationalized by assuming a rapid inversion between syn and anti forms with a temperature-dependent population (67JA1579) (see Table I).

In 5-alkylthianthrenium salts, the 4- and 6-proton signals are pulled downfield by 0.5–0.9 ppm, and in 5-arylthianthrenium salts, the signals are pulled downfield by ~ 0.4 –0.8 ppm. These peri protons are downfield by ~ -47 ppm with respect to CHCl_3 in thianthrene sulfoxides.

C. ^{13}C - AND ^{19}F -NMR SPECTROSCOPY

The three ^{13}C shifts for thianthrene, determined in deuterochloroform solution, are shown in **10** (84CB107), and the fluorine shifts (in ppm relative to trichlorofluoromethane) for perfluorothianthrene, determined in acetone solution, are shown in **11** (68T2783, 68T3997). Other ^{13}C determi-

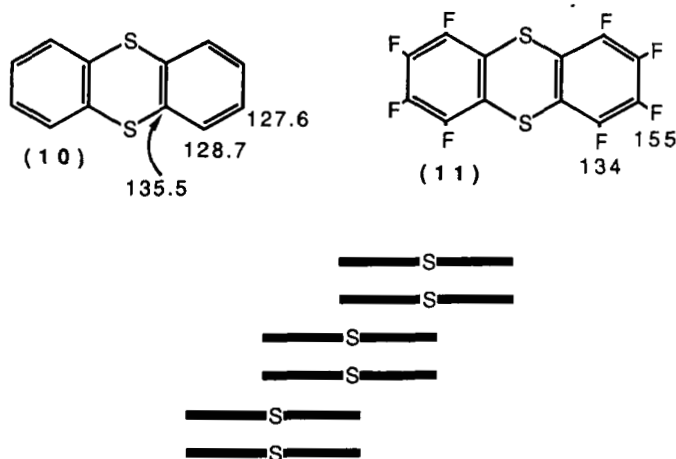


FIG. 4. Arrangement of dimers in the I_3^- salt. (Viewed from side of stack.)

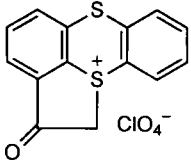
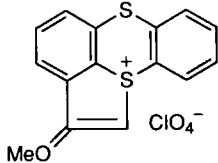
TABLE I
REPRESENTATIVE ¹H-NMR SPECTRA OF THIANTHRENES

Substance	Solvent	δ [integral; multiplicity; coupling constant(s)(J) in Hz; assignment]		Reference
		Ring protons	Other protons	
Thianthrene (T)	CDCl ₃	7.48(4H;ddd;7.9,1.3,0.3; 1-,4-,6-,9-H), 7.23(4H;ddd;7.9,7.4,1.3; 2-,3-,7-,8-H)		740MR115
T	(CHCl ₂) ₂	−90.6 ^a (4H;dd;8.0,1.4; 1-,4-,6-,9-H), −78.2 ^a (4H;ddd;8.0,6.2,1.4; 2-,3-,7-,8-H)		67JA1579
T	CDCl ₃	−14.4 ^b (4H;1-,4-,6-,9-H), 1.0 ^b (4H;2-,3-,7-,8-H)		67JA1579
T	CDCl ₃	−13.3 ^c (4H; 1-,4-,6-,9-H), 1.7 ^c (4H; 2-,3-, 7-,8-H)		67JA1579
1,4,6,9-(Me) ₄ -T ^d	CDCl ₃	7.0(4H;s;2-,3-,7-,8-H)	2.55(12H;s;4 × CH ₃)	71BSF2060
1,3,7,9-(Me) ₄ -T ^d	CDCl ₃	7.1(2H;bs;4-,6-H ^e), 6.8(2H;bs;2-,8-H ^e)	2.2 and 2.4(2 × 3H;2 × s; 2 × CH ₃)	71BSF2060
2,7-(Bu ^t) ₂ -T	— ^f	— ^f (6H, “ABC system; 8.5,1.9,0.6”)	1.3(18H;s;2 × (CH ₃) ₃ C	68CB2956
1,3,6,8-(Bu ^t) ₄ -T	— ^f	7.6(2H;d;2,4-,8-H ^e), 7.4(2H;d;2-,6-H ^e)	1.6 and 1.3(2 × 18H;2 × s; 4 × (CH ₃) ₃ C)	68CB2956
2,7-(EtO ₂ C) ₂ -T	CDCl ₃	8.09 ^g (2H; 1-,6-H), 7.90 ^g (2H; 3-,8-H), 7.49 ^g (2H;4-,9-H)	4.36(4H;q;2 × CH ₂), 1.37(6H;t;2 × CH ₃)	84CB107
2,3,7,8-(EtO) ₄ -T	— ^f	7.0(xH;1-,4-,6-,9-H)	— ^f (4.8 × H;4 × CH ₃ CH ₂ O)	69JCS(D)847
2,3,7,8-(MeO) ₄ -T	CDCl ₃	7.03(4H;s;1-,4-,6-,9-H)	3.88(12H;s;4 × CH ₃ O)	86JCR(M)2801, 86JCR(S)326
2,3,7,8-(OCH ₂) ₂ -T	CDCl ₃	6.93(4H;s;1-,4-,6-,9-H)	5.96(4H;s;2 × (OCH ₂ O))	86JCR(M)280, 86JCR(S)326
2-PhS-T	CDCl ₃	7.58–7.01(12H ^e ,m)		87MI1
2-(2,3-diazabicyclo[2.2.2] oct-2-en-2-yl)-T ClO ₄ -	CD ₂ Cl ₂	8.16(1H;d;2.5), 8.1(1H;dd;2.6, 8.6), 7.8(1H;d;8.6), 7.52(2H;m), 7.35(2H,m)	6.22(1H;br s), 6.01(1H;br s), 2.40(4H;m), 1.92(4H;m)	88JA7880
2,7-(O ₂ N) ₂ -T	NMP ^h	8.81(2H;d;1-,6-H), 8.28(2H;dd;3-,8-H), 8.18(2H;d;4-,9-H)		84ZOR202
2,7-(O ₂ N) ₂ -T	CDCl ₃	8.3–8.0(4H;m;1-,3-,6-,8-H ^e), 7.5(2H;d;4-,9-H ^e)		83SC1181
2,7-(H ₂ N) ₂ -T	(CD ₃) ₂ CO	7.1–6.2(6H;m;1-,3-,4-,6-,8-,9-H ^e)	3.9(4H;bs;2 × H ₂ N ⁵)	83SC1181

311	2,7-Cl ₂ -T	CDCl ₃	7.4(2H;d;1-,6-H ^e), 7.2(4H;m;3-,4-,7-,8-H ^e)	83SC1181
	2,7-(H ₂ N)(O ₂ N)-T	CDCl ₃	8.3–6.6(6H;m;1-,3-,4-,6-,8-,9-H)	83SC1181
	2,7-Cl(O ₂ N)-T	CDCl ₃	8.3–8.0(2H;m;6-,8-H ^e), 7.7–7.3(4H;m;1-,3-,4-,9-H ^e)	83SC1181
	2-O ₂ N-T	CDCl ₃	8.3–8.0(2H;m;1-,3-H ^e), 7.5–7.1(5H;m;4-,6-,7-,8-,9-H ^e)	83SC1181
	1,6-(O ₂ N) ₂ -3,8-(F ₃ C) ₂ -T	THF ^j	8.07(2H;m;2-,7-H), 7.90(2H;m;4-,9-H)	77JOC2896
	5-Bu ⁿ -T ⁺ ClO ₄ ⁻	CH ₂ Cl ₂	8.2(2H;m;4-,6-H ^b), 7.8(6H;m;1-,2-,3-,7-,8-,9-H ^b), 3.7(2H;t;6.5;CH ₂ S ⁺), 1.5(4H;m;CH ₂ CH ₂), 0.8(3H;t;6;CH ₃)	86T6111
	5-(propan-2-on-1-yl)-T ⁺ ClO ₄ ⁻	CDCl ₃ and (CD ₃) ₂ SO	8.36–7.68(8H;m;1-,2-,3-,4-,6-,7-,8-,9-H)	83MI6
	5-(4-NC-C ₆ H ₄ -CH ₂)-T ⁺ CF ₃ SO ₃ ⁻	CD ₃ CN	7.90–7.10(12H; 1-,2-,3-,4-,6-,7-,8-,9-H and C ₆ H ₄)	86T6123
	5-(indan-1-on-2-yl)-T ⁺ ClO ₄ ⁻	(CD ₃) ₂ CO	7.9(12H;m;1-,2-,3-,4-,6-,7-,8-,9-H and C ₆ H ₄)	75JOC3857
	5-(4-Bu ^t -cyclohexan-1-on-2-yl)- T ⁺ ClO ₄ ⁻	CD ₃ CN	7.98(8H;m;1-,2-,3-,4-,6-,7-,8-,9-H)	75JOC3857
	5-(EtO ₂ CCH ₂)-T ⁺ ClO ₄ ⁻	(CD ₃) ₂ SO	7.86(8H;m;1-,2-,3-,4-,6-,7-,8-,9-H)	75JOC3857
	1,2-(T ⁺ -5-yl) ₂ -cyclohexane 2ClO ₄ ⁻	SO ₂ (liq)	8.40–7.60(16H;m;2 × (1-,2-,3-,4-,6-,7-,8-,9-H))	81JOC271
	5-(propen-2-yl)-T ⁺ ClO ₄ ⁻	CDCl ₃ and (CD ₃) ₂ SO	8.55–7.65(8H;m;1-,2-,3-,4-,6-,7-,8-,9-H)	85MI1
	1,2-(T ⁺ -5-yl) ₂ -ethene 2ClO ₄ ⁻	CD ₃ CN	8.24–8.10(4H;m;2 × (4-,6-H ^e), 8.02–7.60[12H;2 × (1-,2-,3-,7-,8-,9-H) ^e]	79JOC915
	1,2-(T ⁺ -5-yl) ₂ -prop-1-ene 2ClO ₄ ⁻	CD ₃ CN	8.34–8.12[4H;m;2 × (4-,6-H ^e)], 8.02–7.62[12H;2 × (1-,2-,3-,7-,8-,9-H) ^e]	79JOC915
	2,3-(T ⁺ -5-yl) ₂ -but-2-ene 2ClO ₄ ⁻	CD ₃ CN	8.34–8.12[4H;m;2 × (4-,6-H ^e)], 8.04–7.68[12H;2 × (1-,2-,3-,7-,8-,9-H) ^e]	79JOC915

(continued)

TABLE I (Continued)

Substance	Solvent	δ [integral; multiplicity; coupling constant(s)(J) in Hz; assignment]		Reference
		Ring protons	Other protons	
1-(C ₆ H ₅) ₂ -1,2-(T ⁺ -5-yl) ₂ -ethene 2ClO ₄ ⁻	CD ₃ CN	8.0–6.84(21H;m;2 × (1-,2-,3-,4-,6-7-,8-9-H) and C ₆ H ₅)	6.52(1H;s;CH : C)	79JOC915
5-(4-Me-C ₆ H ₄)-T ⁺ ClO ₄ ⁻	— ^f	8.3(2H;m;4-,6-H), 7.8(6H;m;1-,2-,3-,7-,8-9-H)	7.1(4H;m;C ₆ H ₄), 0.5(3H;s;CH ₃)	71JOC2923
5-(4-MeO-C ₆ H ₄)-T ⁺ ClO ₄ ⁻	(CD ₃) ₂ SO	8.3(2H;m;4-,6-H), 7.8(6H;m;1-,2-,3-,7-,8-9-H)	7(4H;m;C ₆ H ₄), 1.9(3H;s;CH ₃ O)	71JOC2923
5-(4-NC-C ₆ H ₄)-T ⁺ CF ₃ SO ₃ ⁻	CD ₃ CN	7.90–7.10(12H; 1-,2-,3-,4-,5-,6-,7-,8-,9-H and C ₆ H ₄)	4.90(2H;s;CH ₂ ^e)	86T6123
5-[4-(4-Me-C ₆ H ₄ SO ₂ NH)- C ₆ H ₄]-T ⁺ ClO ₄ ⁻	(CD ₃) ₂ SO	8.5–7.0(16H)	2.37(3H;s;CH ₃)	81MI9
5-(T-2-yl)-T ⁺ ClO ₄ ⁻	CDCl ₃ and (CD ₃) ₂ SO	8.70–8.41(2H;m;4-,6-H), 7.97–6.86(13H;m;1-, 2-,3-,7-,8-,9-,1'-,2'-,3'-,4'-,6'-,7'-,8'-,9'-H),		83MI1
	CD ₃ CN	8.35–7.55(7H;m;1-,2-,3-,6-,7-,8-,9-H)	4.90(2H;s;CH ₂ S ⁺)	80JCS(P1)1185
	CD ₃ NO ₂	8.20–7.55(7H;m;1-,2-,3-,6-,7-,8-,9-H)	3.10(1H;s;HC : C ^e), 5.65(3H;s;CH ₃ O)	80JCS(P1)1185
5-MeNH-T ⁺ ClO ₄ ⁻	CDCl ₃	8.22(2H;dd;ca.7,2;4-,6-H), 7.89–7.57(6H;m;1-, 2-,3-,7-,8-,9-H)	6.24(1H;bs;HN), 2.57(3H;d;CH ₃ N)	77JOC1538

5-Me ₂ N-T ⁺ ClO ₄ ⁻	CDCl ₃	8.34(2H;m;4-,6-H), 7.80(6H;m;1-,2-,3-,7-,8-,9-H)	2.83[6H;s;(CH ₃) ₂ N]	77JOC1538
5-Me ₂ N-T ⁺ I ⁻	CDCl ₃	8.67(2H;m;4-,6-H), 7.83(6H;s;1-,2-,3-,7-,8-,9-H)	2.90[6 ^e H;s;(CH ₃) ₂ N]	77JOC1538
5-EtNH-T ⁺ ClO ₄ ⁻	CD ₃ CN	8.19(2H;dd;ca.7,2;4-,6-H), 7.93–7.57(6H;m;1-,2-,3-,7-,8-,9-H)	2.96(2H;q;7.5;CH ₂), 1.02(3H;t;7.5;CH ₃)	77JOC1538
5-C ₆ H ₅ CH ₂ (CH ₃)N-T ⁺ ClO ₄ ⁻	CDCl ₃ and CD ₃ CN	8.15(2H;dd;4-,6-H), 7.87(6H;m;1-,2-,3-,7-,8-,9-H)	7.51–7.27(5H;m;C ₆ H ₅), 3.33(2H;s;CH ₂), 2.55(3H;s;CH ₃)	77JOC1538
5-MeO-1-(2-Br-1-MeO-ethen-1-yl)-T ⁺ ClO ₄ ⁻	CD ₃ NO ₂	8.35–7.60(7H;m;2-,3-,4-,6-,7-,8-,9-H)	7.50(1H;s;C : CH), 3.65(3H;s;CH ₃ O), 3.35(3H;s;CH ₃ O)	80JCS(P1)1185
2,3,7,8-(MeO) ₄ -T ²⁺	CH ₃ NO ₂ and AlCl ₃	8.4(broad)(4H;1-,4-,6-,9-H)	6.6(broad)(12H;4xCH ₃ O)	73JA2375
5,5-H ₂ -5-Bu ¹ CO.C : T	CDCl ₃	7.44(8H;m;1-,2-,3-,4-,6-,7-,8-,9-H)	4.06(1H;s;HC : C), 1.35[9H;s;(CH ₃) ₃ C]	75JOC3857
5,5-H ₂ -5-naphth-2'-yl-CO.CH : T	CDCl ₃	7.86(15H;m;1-,2-,3-,4-,6-,7-,8-,9-H and C ₁₀ H ₇)	4.76(1H;s;HC : C)	75JOC3857
5,5-H ₂ -5-(EtO ₂ C)(CH ₃ CO)CH : T	CDCl ₃	7.47(8H;m;1-,2-,3-,4-,6-,7-,8-,9-H)	4.14(2H;q;CH ₂ O), 2.70(3H;s;CH ₃), 1.03(3H;t;CH ₃)	75JOC3857
5,5-H ₂ -5-CH ₃ N : T	CDCl ₃	7.90(2H;dd;ca.6,2;4-,6-H), 7.66–7.25(6H;m;1-,2-,3-,7-,8-,9-H)	2.78(3H;s;CH ₃ N)	77JOC1538
5,5-H ₂ -5-C ₆ H ₅ CH ₂ N : T	CDCl ₃	7.90(2H;dd;4-,6-H), 7.69–7.17(11H;m;1-,2-,3-,7-,8-,9-H and C ₆ H ₅)	4.23(2H;s;CH ₂)	77JOC1538
5,5-H ₂ -5-MeSO ₂ N : T	(CD ₃) ₂ SO	8.20–7.82(2H;m;4-,6-H), 7.81–7.46(6H;m;1-,2-,3-,7-,8-,9-H)	3.26(3H;s;CH ₃)	83MI1
5,5-H ₂ -5-PhSO ₂ N : T	(CD ₃) ₂ SO	8.10–7.75(2H;m;4-,6-H), 7.75–7.43(11H;m;1-,2-,3-,7-,8-,9-H and C ₆ H ₅)		83MI1
5,5-H ₂ -5-(T ⁺ -5-yl : N)-T ClO ₄ ⁻	(CD ₃) ₂ SO	8.0(4H;m;4-,4'-,6-,6'-H), 7.6(12H;m;1-,2-,3-,7-,8-,9-,1'-,2'-,3'-,7'-,8'-,9'-H)		72JA1026

(continued)

TABLE I (Continued)

	Substance	Solvent	δ [integral; multiplicity; coupling constant(s)(J) in Hz; assignment]		Reference
			Ring protons	Other protons	
314	5,5-H ₂ -5,5-(1,1,1,3,3,3-F ₆ -2-C ₆ H ₅ -2-propoxy)-T	CCl ₄	7.51(3.8H;d;9); 7.34(2H;t;7.5); 7.11(11.3H;m)		77JOC3222
	5-(1,2-(NC) ₂ -3,5-(EtO ₂ C) ₂ -cyclopentadienid-4-yl)-T ⁺	CDCl ₃	7.47(8H;m;1-,2-,3-,4-,6-,7-,8-,9-H)	4.04(4H;q;2xCH ₂), 1.08(6H;t,2xCH ₃)	79CB1267
	<i>cis</i> -T-5,10-(O) ₂	CDCl ₃	−47.2 ^k (4H;1-,4-,6-,9-H), −28.0 ^k (4H;2-,3-,7-,8-H)		67JA1579
	<i>cis</i> -T-5,10-(O) ₂	CDCl ₃	−48.6 ^c (4H;1-,4-,6-,9-H), −25.4 ^c (4H;2-,3-,7-,8-H)		67JA1579
	<i>cis</i> -T-5,10-(O) ₂	(Cl ₂ CH) ₂	−119.7 ⁱ (4H;dd;7.6,1.3;1-,4-,6-,9-H), −104.3 ⁱ (4H;ddd;7.6,6.6,1.3;2-,3-,7-,8-H)		67JA1579
	<i>cis</i> -T-5,10-(O) ₂	(Cl ₂ CH) ₂	−120.9 ^m (4H;1-,4-,6-,9-H), −104.1 ^m (4H;2-,3-,7-,8-H)		67JA1579
	<i>cis</i> -T-5,10-(O) ₂	(Cl ₂ CH) ₂	−125.2 ⁿ (4H;1-,4-,6-,9-H), −104.0 ⁿ (4H;2-,3-,7-,8-H)		67JA1579
	<i>cis</i> -T-5,10-(O) ₂	(Cl ₂ CH) ₂	−127.0 ^o (4H;1-,4-,6-,9-H), −104.5 ^o (4H;2-,3-,7-,8-H)		67JA1579
	<i>trans</i> -T-5,10-(O) ₂	(Cl ₂ CH) ₂	−126.6 ^p (4H;dd;7.4,1.2;1-,4-,6-,9-H), −101.4 ^p (4H;ddd;8.0,7.4,1.2;2-,3-,7-,8-H)		67JA1579
	<i>trans</i> -T-5,10-(O) ₂	(Cl ₂ CH) ₂	−126.8 ^q (4H;1-,4-,6-,9-H), −101.2 ^q (4H;2-,3-,7-,8-H)		67JA1579

T-5,5-(O) ₂	CDCl ₃	8.32–8.15(2H;m;4-,6-H ^e), 7.68–7.40(6H;m;1-, 2-,3-,7-,8-,9-H ^e)		85MI1
2,8-(MeO ₂ C) ₂ -T-10-O ^d	CDCl ₃ and Eu(fod) ₃	10.4(2H;bd;1-,9-H), 8.61(2H;dd;3-,7-H), 7.90(2H;d;4-,6-H)	4.05(6H;s;2xCH ₃ O)	77TL2643
2,7-(MeO ₂ C) ₂ -T-5-O ^d	CDCl ₃ + Eu(fod) ₃	13.0(1H;bs;6-H), 10.65(1H;d;4-H), 8.98(1H;dd;1-H), 8.89(1H;d;3-H), 8.59(1H;dd;8-H), 8.24(1H;d;9-H)	4.05 and 4.15 (2x3H;2xs; 2xCH ₃ O)	77TL2643
η ⁶ -2-Me-T-η ⁵ -C ₅ H ₅ Fe ⁺ PF ₆ ⁻	(CD ₃) ₂ CO	7.26(7H;m;1-,3-,4-,6-,7-,8-,9-H)	2.26(3H;s;CH ₃)	82JHC801
cis-η ⁶ , η ⁶ -T-(η ⁵ -C ₅ H ₅ Fe ⁺) ₂ 2AsF ₆ ⁻	(CD ₃) ₂ CO and (CD ₃) ₂ SO	6.95(4H;m), 6.54(4H;m)	5.28(10H;s;2xC ₅ H ₅)	83JOM357
trans-η ⁶ , η ⁶ -T-(η ⁵ -C ₅ H ₅ Fe ⁺) ₂ 2AsF ₆ ⁻	(CD ₃) ₂ CO and (CD ₃) ₂ SO	6.95(4H;m), 6.54(4H;m)	5.05(10H;s;2xC ₅ H ₅)	83JOM357

^a In cps relative to solvent (0 cps) at 40°C or 100°C.

^b In cps relative to CHCl₃ (0 cps) at 40°C.

^c In cps relative to CHCl₃ (0 cps) at 100°C.

^d δ values estimated from published diagram.

^e Reviewer's assignments.

^f Not specified.

^g Signals comprise "ABC system."

^h NMP = *N*-methylpyrrolidone.

ⁱ NH₂ signal "not observed."

^j THF = tetrahydrofuran.

^k In cps relative to CHCl₃ (0 cps) at –20°C.

^l In cps relative to solvent (0 cps) at –40°C.

^m In cps relative to solvent (0 cps) at –20°C.

ⁿ In cps relative to solvent (0 cps) at 100°C.

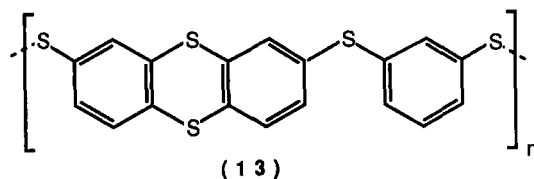
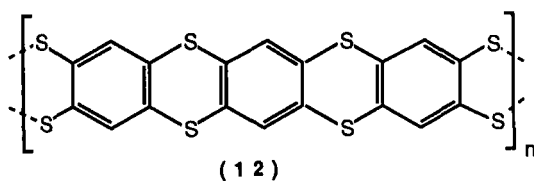
^o In cps relative to solvent (0 cps) at 160°C.

^p In cps relative to solvent (0 cps) at 40°C.

nations are given in Table II; the ^{19}F spectra of 2-methoxy-1,3,4,6,7,8,9-heptafluorothianthrene (68T2783, 68T3997) and 1,4,6,9-tetrafluoro-2,3,7,8-tetrakis(trifluoromethyl)thianthrene (72T105) have been recorded.

D. INFRARED SPECTROSCOPY

Infrared spectroscopy is of limited value in the characterization of thianthrenes (71MI1), though a comparison of intensities for peaks at 875 and 805 cm^{-1} , for the out-of-plane bendings corresponding to isolated and adjacent hydrogens, respectively, was used to estimate the ratio of ladder-polymer **12** and polymer **13** in a mixture (85MI2; 88MI3).



More structural information can be gained from IR examination of thianthrene oxides and dioxides. Thus, for *cis*-thianthrene 5,10-dioxide, the two equatorial S—O bonds have a stretching frequency at 1088 cm^{-1} in CHCl_3 , 1095 cm^{-1} in CCl_4 ; and 1075 cm^{-1} in KBr disc (84BCJ2526). In the *trans*-isomer, in which one S—O bond is axial, there is a marked difference: Axial, 1044 cm^{-1} in CHCl_3 ; (1059 cm^{-1} in CCl_4); and for equatorial, 1075 cm^{-1} in CHCl_3 ; 1080 cm^{-1} in CCl_4 ; 1085 cm^{-1} in KBr disc (84BCJ2526). Stretchings are clearly diagnostic (64SA159). (See also under UV/Vis Spectroscopy.) More generally, the stretching frequency for several (equatorial) *cis*-thianthrene 5,10-dioxides in KBr is in the range 1087–1044 cm^{-1} , the values for (axial and equatorial S—O stretchings) *trans*-5,10-dioxides being 1018–1044 and 1070–1079 cm^{-1} , respectively (64JA2957). The *cis*-5,10-dioxide S—O frequency is shifted to 1037 cm^{-1} , in the presence of iodine, and to 1005 cm^{-1} by adding ICl. The *trans*-isomer similarly reflects complexation, showing 995 and 991 cm^{-1} with the addition of ICl (77JOC2010). Cadmium and mercury halides have also

TABLE II
REPRESENTATIVE ^{13}C -NMR SPECTRA^a OF THIANTHRENES

Substance	δ Values for ring carbons											Reference	
	1	2	3	4	4a	5a	6	7	8	9	9a		10a
Thianthrene (T)	128.7	127.6	127.6	128.7	135.5	etc							84CB107
2,7-(MeO ₂ C) ₂ -T ^d	129.5	130.0	128.9	128.4	140.5	etc						134.6	84CB107
2-Br-T	131.1	121.5	130.5	129.6	134.6	135.1 ^b	128.7	127.6 ^c	127.9 ^c	128.7	135.3 ^b	137.6	84CB107
2,3,7,8-(MeO) ₄ -T	111.9	148.8	148.8	111.9	127.6	etc							86JCR(M)
													2801,86JCR
													(S)326
2,3,7,8-(OCH ₂ O) ₂ -T	109.1	148.0	148.0	109.1	129.3	etc							86JCR(M)
													2801,86JCR
													(S)326
2-(2,3-diazabicyclo[2.2.2]oct-2-en-2-yl-T ClO ₄ ⁻	147.8, 142.9, 139.3, 133.0, 130.4, 129.3, 129.25, 129.2, 129.1, 122.0, 121.8, 69.1, 68.4, 26.0, 24.4 ^{7g}												88JA7880
<i>cis</i> - η^6 , η^6 -T-(η^5 -C ₅ H ₅ Fe ⁺) ₂ AsF ₆ ^{-e,f}	101.2(s), 87.0(d), 88.2(d) ^{g,h}												83JOM357
<i>trans</i> - η^6 , η^6 -T-(η^5 -C ₅ H ₅ Fe ⁺) ₂ AsF ₆ ^{-e,f,i}	103.3(s), 86.6(d), 86.4(d) ^{g,h}												83JOM357
5-C ₆ H ₅ -T ⁺ AsF ₆ ^{-j}	134.8	135.6	128.0	129.6	119.2	etc						135.6	80MI8

^a In CDCl₃ solution.

^b Signals interchangeable.

^c Signals interchangeable.

^d Other signals: 165.8(C: O), 52.3(CH₃).

^e In d₆-DMSO

^f Other signal: 79.5(C₅H₅).

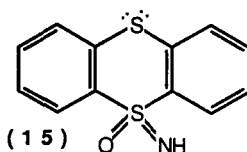
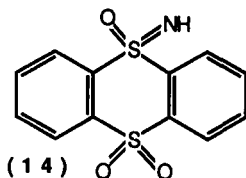
^g No signal assignments made.

^h s, singlet; d, doublet.

ⁱ Other signal: 80.3(C₅H₅).

^j Other signals: 124.8(1-C of C₆H₅), 130.3(2×2-C of C₆H₅), 130.5(2×3-C of C₆H₅), 132.6(4-C of C₆H₅).

been employed for the production of diagnostically useful shifts. In nujol, addition of mercury (II) chloride shifted the S—O stretch in thianthrene 5-oxide by 22 cm^{-1} ($1077 \rightarrow 1055$); the equatorial stretchings in thianthrene 5,10-dioxide shifted by 19 cm^{-1} ; the equatorial S—O stretch in the *trans*-5,10-dioxide shifted by 15 cm^{-1} ; and the axial stretch shifted by 58 cm^{-1} [74SA(A)2021]. In the reverse sense, a shift in S—O frequency was used as evidence for metal coordination via oxygen (rather than sulfur) in the interaction of thianthrene 5-oxide with molybdenum(V) chloride (72MI2) and uranyl halides [76IJC(A)135]. Rather different values were reported for the S—O stretch in sulfoximines **14** (1040 cm^{-1}) (74JHC839) and **15** (1240 cm^{-1}) (74TL1973).



Values of 3066 (very weak) and 762 (strong), 754 (medium), and 731 (weak) cm^{-1} were recorded for both *cis*- and *trans*-thianthrene 5,10-dioxides for C—H bending and stretching, respectively (64SA159).

E. ULTRAVIOLET/VISIBLE SPECTROSCOPY, FLUORESCENCE, AND PHOSPHORESCENCE

The absorption maxima for representative substituted thianthrenes and for thianthrenium ions are given in Table III; Table IV gives representative values for thianthrene radical ions(1+) and for thianthrenediiums. Thianthrene itself shows $\lambda_{\text{max}} = 242, 257, \text{ and } 275$ sharp (sh) ($\log \epsilon = 4.16, 4.56, \text{ and } 3.31$) in ethanol and the absorption obeys the Beer–Lambert law within the absorbance range 0.05–0.6 l (79JCP305). A single, 1 mm thick crystal of thianthrene starts absorbing at 365 nm and absorbs intensely from 360 nm downwards; a thinner crystal had absorption from 295 to 240 nm, with a maximum at 273 nm (85MI8). A solution-state study of the emission spectrum of thianthrene, demonstrated the production of transients emitting at 287 and 475 nm. From this and other data, the emission was ascribed to a triplet (66AC10; 73JPC1478). The emission spectrum of a single crystal, excited at 300 nm, ranged from 400 to 560 nm with a maximum at 460 nm; at 77 K the emission was much more intense, with $\lambda_{\text{max}} = 450\text{ nm}$ (81MI8).

A self-trapping mechanism for singlet and triplet excitons, ascribed to

changes in the dipole moment in the singlet versus the triplet state of thianthrene, was demonstrated in other studies in solid and solution phases and in a rigid glass (75MI2). Another study of the first excited and triplet states compared the probability of phosphorescence in thianthrene with that in other chalcanthrenes (77MI4); excitation at 285 nm produces phosphorescence at 480 nm (66AC10). Thianthrene quenches the excited doublet of tris(pentachlorophenyl)methyl radical at a diffusion-controlled rate (87JA7088).

Values for electronic absorption in nonplanar molecules, calculated using the Pariser–Parr–Pople (PPP) method and based on a model excluding sulfur d orbitals, have been correlated with experimental values (70BCJ3929; 72BCJ1589). Charge-transfer absorption was demonstrated in mixtures of thianthrene with sulfur dioxide [$\lambda_{\max} = 395$ nm (75TL1193)]; tetracyanoethene [$\lambda_{\max} = 470$ and 602 nm (66BBA482; 82CJC862)]; 1,2,4,5-tetracyanobenzene [$\lambda_{\max} = 424$ nm (70JMC922)]; 11,11,12,12-tetracyanoanthraquinodimethane [“brownish” (84JOC5002)]; iodine [$\lambda_{\max} = 371$ nm (64JA164; 66BBA482)]; chloranil [$\lambda_{\max} = 418$ and 520 nm (64JA164)]; 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) [$\lambda_{\max} = 534$ and 689 nm (66BBA482)]; pyromellitic anhydride [“orange” (78G21)]; and 2,5-dichloro-*p*-benzoquinone [$\lambda_{\max} = 450$ nm (66BBA482)].

Provided both stereoisomers are available, it is possible to use UV spectroscopy to differentiate *cis*- from *trans*-thianthrene 5,10-dioxides (see also Section II,D): a *trans*-isomer absorbs at longer wavelength, by ~ 10 nm, than the corresponding *cis*-isomer, and the absorption peak is sharper (64JA2957).

The magenta appearance of the paramagnetic solution produced by dissolving thianthrene in *c.* sulfuric acid is due to the absorbance of the thianthrene radical ion(1+) ($T^{\cdot+}$) (4) formed by one-electron oxidation. Even before this was understood, the formation of such deep colors on dissolution in *c.* sulfuric acid was used as a diagnostic test for a thianthrene ring system.

The absorption of thianthrene radical ion(1+) shows good linearity with concentration and has been developed into an analytical method for the determination of thianthrenes (mainly 2,7-dimethylthianthrene) in the commercial antiparasitic, mesulfen (80MI5). The principal absorption maximum of thianthrene radical ion(1+) in the visible region is at ~ 545 nm ($\log \epsilon 3.95$); the value varies slightly with solvent, concentration, and counterion with two other peaks in the near infrared at 920 and 1050 nm of low intensity (62JA4798). Thus, 543 nm ($\log \epsilon 3.08$) was given for thianthrene radical ion(1+) perchlorate in propionitrile in dilute solution. At higher concentration and at -80°C , absorption maxima at 470 nm ($\log \epsilon 3.54$) and 594 nm ($\log \epsilon 3.74$), and an observed diamagnetism, were inter-

TABLE III
REPRESENTATIVE UV/VISIBLE SPECTRA OF THIANTHRENES AND THIANTHRENIUM IONS

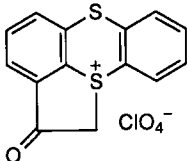
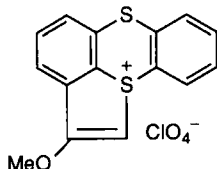
Substance	Solvent	λ_{max} (nm) ^a	log ϵ	Reference
Thianthrene(T)	EtOH	257	4.56	79JCP305
T	Heptane	209sh, 243sh, 254sh, 258	— ^b — ^b — ^b , 4.6	66MI3
2,7-(Ph.CH:CH) ₂ -T	EtOH	329	4.88	69HCA1282
2-(Pyridinium-1-yl)-T ClO ₄ ⁻	CH ₃ CN	255	4.36	72JOC2691
2-(2,3-Diazabicyclo[2.2.2] oct-2-en-2-yl)-TCIO ₄ ⁻	CH ₂ Cl ₂	408, 480sh	3.74, 3.58	88JA7880
6,9-(HO) ₂ -2,3,7,8-(Me) ₄ -T- 1,4-dione	THF ^c	438	3.78	69CB1739
2,3,7,8-(Me) ₄ -T-1,4,6,9- tetrone	THF ^c	521	3.72	69CB1739
5-(propan-2-on-1-yl)-T ⁺ ClO ₄ ⁻	CH ₃ OH	224(broad), 290(broad)	— ^b	83MI6
5-(Indan-1-on-2-yl)-T ⁺ ClO ₄ ⁻	CH ₃ CN	243, 255, 291(broad)	4.40, 4.61, 3.61	75JOC3857
5-(4-Bu ⁻ -cyclohexan-1-on-2- yl)-T ⁺ ClO ₄ ⁻	CH ₃ CN	225, 255, 290— 312(broad)	4.65, 4.38, 3.98	75JOC3857
	CH ₃ OH	211, 255sh, 282sh, 326sh	4.69,— ^b — ^b — ^b	80JCS(P1)1185
5-(Propen-2-yl)-T ⁺ ClO ₄ ⁻	CH ₃ CN	222, 260, 307	4.34, 3.68, 3.74	85MI1
	CH ₃ OH	211, 266sh, 250, 314	4.39, 4.27, 4.10, 3.4	80JCS(P1)1185
5-(C ₆ H ₅)-T ⁺ ClO ₄ ⁻	— ^b	225, 310	4.50, 3.88	71JOC2923
5-(C ₆ H ₅)-T ⁺ ClO ₄ ⁻	CH ₃ OH	260sh, 305 ^d	— ^b	80MI8
5-(4-Me-C ₆ H ₄)-T ⁺ ClO ₄ ⁻	CH ₃ CN	227, 310	4.51, 3.81	71JOC2923
5-(4-Me-C ₆ H ₄)-T ⁺ ClO ₄ ⁻	CH ₃ OH	225, 307	4.50, 3.76	85MI5
5-[4-(4-Me-C ₆ H ₄ SO ₂ NH)- C ₆ H ₄]-T ⁺ ClO ₄ ⁻	C ₂ H ₅ OH	220sh, 264, 315sh	8 ^b	81MI9
5-(4-H ₂ NC ₆ H ₄)-T ⁺ ClO ₄ ⁻	CH ₃ CN	265, 299	3.20, 3.36	74JOC2534
5-(4-Me ₂ NC ₆ H ₄)-T ⁺ ClO ₄ ⁻ 2H ₂ O	CH ₃ CN	223, 316	4.72, 4.51	74JOC2534
5-(4-AcNHC ₆ H ₄)-T ⁺ ClO ₄ ⁻	CH ₃ CN	283	4.20	74JOC2534
5-(4-HOC ₆ H ₄)-T ⁺ ClO ₄ ⁻	CH ₃ CN	267sh, 316(broad)	4.00, 4.38	74JOC2534

TABLE III (continued)

Substance	Solvent	λ_{\max} (nm) ^a	log ϵ	Reference
5-(4-MeO-C ₆ H ₄)-T ⁺ ClO ₄ ⁻	CH ₃ CN	247, 310	4.20, 4.73	71JOC2923
5-(3-Bu ¹ -4-HOC ₆ H ₄)-T ⁺ ClO ₄ ⁻	CH ₃ CN	256, 283, 313	4.18, 4.04, 3.83	74JOC2534
5-(3-Cl-4-HOC ₆ H ₄)-T ⁺ ClO ₄ ⁻	CH ₃ CN	250, 289, 316	4.18, 4.00, 3.93	74JOC2534
5-(T-2-yl)-T ⁺ ClO ₄ ⁻	C ₂ H ₅ OH	229, 270, 317	— ^b	83MI1
5-MeNH-T ⁺ ClO ₄ ⁻	CH ₃ CN	221, 253, 294, 328	4.36, 4.08, 3.91, 3.91	77JOC1538
5-Me ₂ N-T ⁺ ClO ₄ ⁻	CH ₃ CN	222, 255, 298, 330	4.45, 3.99, 3.89, 3.65	77JOC1538
5-Me(Pr ⁿ)N-T ⁺ ClO ₄ ⁻	CH ₃ CN	225, 244, 298, 334	4.54, 4.44, 3.99, 3.72	77JOC1538
5-Carbazol-9-yl-T ⁺ ClO ₄ ⁻	CH ₃ CN	275, 318sh	4.63, 3.81	74JOC2537
5-MeO-1-(2-Br-1-MeO-ethen-1-yl)-T ⁺ ClO ₄ ⁻	— ^b	212sh, 218sh, 223, 242sh, 258, 305	4.26, 4.29, 4.31, 4.16, 3.99, 3.52	80JCS(PI)1185
5,5-H ₂ -5-Bu ¹ CO.C : T	CH ₃ CN	238, 249, 286	3.72, 3.67, 3.32	75JOC3857
5,5-H ₂ -5-(EtO ₂ C) (CH ₃ CO)C : T	CH ₃ CN	236	4.44	75JOC3857
5,5-H ₂ -5-MeN : T	CH ₃ CN	216, 259, 285sh, 325sh	4.42, 4.29, 4.21, 3.56	77JOC1538
5,5-H ₂ -5-C ₆ H ₁₁ N : T	CH ₃ CN	242, 285, 333	4.14, 3.63, 2.90	77JOC1538
5,5-H ₂ -5-Bu ¹ N : T	CH ₃ CN	249, 288(broad)	3.26, weak	74JOC2537
5,5-H ₂ -5-MeSO ₂ N : T	C ₂ H ₅ OH	228, 287	4.48, 3.71	83MI1
5,5-H ₂ -5-PhSO ₂ N : T	C ₂ H ₅ OH	227, 287	4.23, 287	83MI1
5,5-H ₂ -5-(T ⁺ -5-yl)N : T ClO ₄ ⁻	CH ₃ CN	227, 291, 335	3.63, 3.04, 2.70	72JA1026
<i>cis</i> -T-5,10-(O) ₂ ⁴	95% EtOH	212, 255sh	4.72, 3.70	64JA2957
<i>trans</i> -T-5,10-(O) ₂ ⁴	95% EtOH	221, 255, 268, 277	4.74, 3.70, 3.70, 3.70	64JA2957
T-5,5-(O) ₂	CH ₃ OH	226, 261, 282, 318	— ^b	85MI1
<i>cis</i> -2,7-(Me) ₂ -T-5,10-(O) ₂ ⁴	95% EtOH	216, 257	4.72, 3.78	64JA2957
<i>trans</i> -2,7-(Me) ₂ -T-5,10-(O) ₂ ⁴	95% EtOH	228, 257, 271, 280	4.76, 3.78, 3.70, 3.70	64JA2957
<i>cis</i> -2-(MeO ₂ C)-T-5,10-(O) ₂ ⁴	95% EtOH	222	4.61	64JA2957
<i>trans</i> -2-(MeO ₂ C)-T-5,10-(O) ₂ ⁴	95% EtOH	226, 275	4.63, 3.90	64JA2957
<i>cis</i> -2-Br-T-5,10-(O) ₂ ⁴	95% EtOH	220, 258	4.66, 3.78	64JA2957
<i>trans</i> -2-Br-T-5,10-(O) ₂ ⁴	95% EtOH	228, 260, 276sh	4.74, 3.85, 3.70	64JA2957
<i>cis</i> -2,7-Cl ₂ -T-5,10-(O) ₂ ⁴	95% EtOH	220	4.72	64JA2957
<i>trans</i> -2,7-Cl ₂ -T-5,10-(O) ₂ ⁴	95% EtOH	234, 263sh	4.79, 3.85	64JA2957

^a sh, Shoulder.^b Not specified.^c THF, tetrahydrofuran.^d λ_{\max} and log ϵ values estimated from published diagram.

TABLE IV
REPRESENTATIVE UV/VISIBLE AND NEAR IR SPECTRA OF THIANTHRENE RADICAL IONS (1+) AND THIANTHRENE DIIUMS

Substance	Solvent	$\lambda_{\max}(\text{nm})^a$	$\log \epsilon$	Reference
Thianthrene radical ion(1+) ^b (T ^{•+})	96% H ₂ SO ₄	270, 290, 546, 920, 1050	4.49, 4.58, 3.95, 2.5 ^c , 2.5 ^c	62JA4798; 64JOC21
T ^{•+}	95% H ₂ SO ₄	263sh, 270, 282sh, 290, 546	— ^d , 4.5, — ^d , 4.58, 3.95	66MI3
T ^{•+}	30% H ₂ SO ₄	546, 833, 917	— ^d , — ^d , — ^d	86ZOR820
2,7-Me ₂ -T ^{•+} + ^b	96% H ₂ SO ₄	273, 295, 580	4.41, 4.64, 4.09	64JOC21
2,7-Bu ₂ -T ^{•+} + ^b	96% H ₂ SO ₄	273, 296, 585	4.45, 4.66, 4.11	64JOC21
1-HO ₂ C-T ^{•+} + ^b	96% H ₂ SO ₄	274, 291, 537	— ^d , 4.65, 4.03	64JOC21
2-HO ₂ C-T ^{•+} + ^b	96% H ₂ SO ₄	300, 534	4.67, 3.98	64JOC21
1-Cl-T ^{•+} + ^b	96% H ₂ SO ₄	274, 291, 299sh, 539	4.49, 4.45, 4.40, 3.93	64JOC21
2-Cl-T ^{•+} + ^b	96% H ₂ SO ₄	274, 294, 572	4.50, 4.69, 4.04	64JOC21
2-Br-T ^{•+} + ^b	96% H ₂ SO ₄	275, 295, 584	4.51, 4.72, 4.07	64JOC21
2,7-Cl ₂ -T ^{•+} + ^b	96% H ₂ SO ₄	276, 297, 585	4.44, 4.70, 4.13	64JOC21
2,7-Br ₂ -T ^{•+} + ^b	96% H ₂ SO ₄	277, 300, 600	— ^d , — ^d , — ^d	64JOC21
1-H ₂ N-T ^{•+} + ^b	96% H ₂ SO ₄	271, 290, 539	4.39, 4.42, 3.72	64JOC21
2-H ₂ N-T ^{•+} + ^b	96% H ₂ SO ₄	274sh, 290, 524	— ^d , 4.70, 3.99	64JOC21

1-HO-T ^{•+} + ^b	96% H ₂ SO ₄	281, 296(broad), 515	4.37, 4.40, 3.89	64JOC21
2-HO-T ^{•+} + ^b	96% H ₂ SO ₄	291, 318, 592	4.74, 4.41, 3.98	64JOC21
2,7-(HO) ₂ -T ^{•+} + ^b	96% H ₂ SO ₄	296, 333, 540	4.41, 4.73, 4.04	64JOC21
2,3,7,8-(MeO) ₄ -T ^{•+}	CH ₃ NO ₂ and MgClO ₄	765	— ^d	73JA2375
2,3,7,8-(MeO) ₄ -T ^{•+}	CH ₃ NO ₂ and 1% TFAA ^e and Et ₄ N ⁺ CF ₃ SO ₃ ⁻	840	4.0	77CJC766
2,3,7,8-(MeO) ₄ -T ^{•+} SbCl ₆ ⁻	KBr disc	270 ^c , 800 ^c , 1500sh ^c	— ^d	87ZN(B)169
2,3,7,8-(MeO) ₄ -T ^{•+} I ₃ ⁻	KBr disc	230sh ^c , 260sh ^c , 305sh ^c , 400sh ^c , 700sh ^c	— ^d	87ZN(B)169
Thianthrenediium (T ²⁺)	100% H ₂ SO ₄	311, 502 ^f	— ^d	66TL1591
T ²⁺	SO ₂ (liq)	“deep red”	— ^d	79JA2316
2,3,7,8-(MeO) ₄ -T ²⁺	CH ₃ CN and 1% TFAA ^e and 0.1M Et ₄ N ⁺ CF ₃ SO ₃ ⁻	710	4.15	77CJC766

^a sh, Shoulder.

^b λ_{max} and log ε values for solutions 3, 4, or 5 days old; complete conversion to radical ion (1+) assumed.

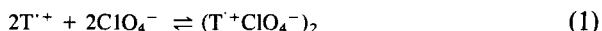
^c Estimated from published diagram.

^d Not given.

^e TFAA, trifluoroacetic anhydride.

^f The absorption produced initially by dissolving thianthrene 5-oxide in 100% sulfuric acid, ascribed to thianthrenediium

puted as aggregation of the radicals according to Eq. (1). Less aggregation was observed in trifluoroacetic acid (TFA) solution



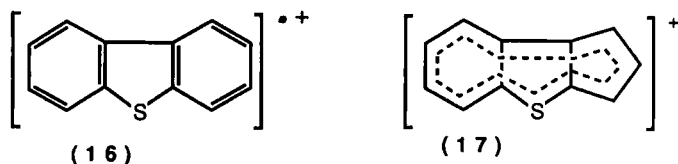
dissociated and
paramagnetic

associated and
diamagnetic

(72JPC3468; 75JA101). A maximum at 548.5 nm was reported for thianthrene radical ion(1+) in methylene dichloride/TFA (85TL1765), and 546 nm was reported in 96% sulfuric acid (64JOC21). A reported maximum of 581 nm in *c.* sulfuric acid/acetic acid (80MI5) is somewhat at variance with other values. MO-LCAO calculations (82PS107; 86RRC649) correlate well with the observed absorption, though whether this can be taken as good evidence for the planarity of thianthrene radical ion(1+), as was assumed in the calculations (82PS107), is less certain, and this fascinating structural question should await other experimental confirmation. The absorption of solid thianthrene radical ion(1+) pentachloroantimonate (69BCJ548) and the reflectance spectra of the perchlorate and pentachloroantimonate salts have also been measured (62JCS4963).

F. MASS SPECTROMETRY

Molecular ions obtained from thianthrenes are normally the base peak in their mass spectra. The principal fragmentation involves loss of sulfur (87PS377), and this is interpreted as formation of a dibenzothiophen radical cation (16). Further loss of sulfur then occurs. CSH is lost from both the dibenzothiophen fragment ion and from the molecular ion; species such as 17, from the parent ion, are proposed (74JHC287). The mass spectroscopic fragmentation pattern of fluorothianthrenes is comparable (72OMS373).

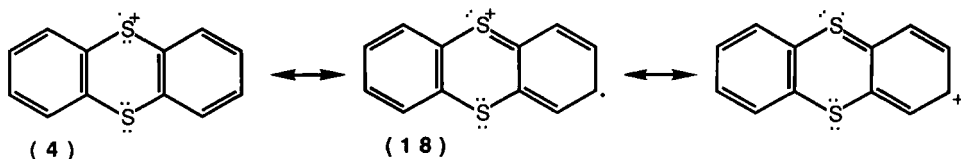


Sulfoxides and sulfones similarly give fragment ions showing loss of SO and SO₂ (68T3255). Interestingly, base peaks for both *cis*- and *trans*-5,10-dioxides were at *m/z* 184, corresponding to dibenzothiophen, i.e. representing overall loss of SO₂ (84BCJ2526)!

G. ELECTRON-SPIN RESONANCE SPECTROSCOPY

Electron-spin resonance (ESR) spectroscopy has been used extensively in studies of the thianthrene radical ion(1+), T^{+} . Early work (62BCJ1040) used the signal as a means for identifying and proving the formation of T^{+} ; later, hyperfine couplings were interpreted (63JCP569; 68JPC1390; 82CB2548), aided by studies of substituted thianthrene radical ions(1+), and observed spin densities correlated with theory (66MI3; 76G457). Later calculations using the unrestricted Hartree-Fock method assumed that T^{+} is nonplanar (80RRC631). A full compilation of ESR data, for T^{+} and a range of substituted thianthrene radical ions(1+), has been published [81MI11; see also 82CB2548 for diagrams and for 2,7-dimethyl- and 2,7-dimethoxythianthrene radical ions(1+) in $CH_2Cl_2-AlCl_3$] and is not duplicated here.

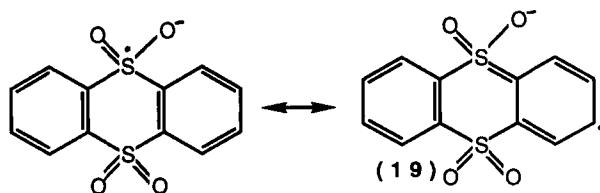
A five-line ESR spectrum is normally observed for the thianthrene radical ion(1+), T^{+} , with a g value of 2.0081; the multiplicity results from coupling to the 2-, 3-, 7-, and 8-protons. Coupling constants (a^H) of 0.013, for protons-1, -4, -6, and -9, and 0.128, for the other four equivalent protons, were determined by measuring T^{+} , at $-51^\circ C$, generated using aluminum chloride in nitromethane (68JA3618, 68JPC1390). A coupling constant (a^S) of 0.915 was also determined for natural abundance ^{33}S . The T^{+} spin density resides, then, principally at sulfur and to a small extent at C-2, -3, -6, and -7, but hardly at all at carbons-1, -4, -6, -7 and -9. To what extent this is illustrated by resonance form **18** is open to question. For,



appreciable contributions from such structures as these would imply planarity; firm establishment of the fold angle in thianthrene radical ion(1+) itself must await further experimental data. However, two salts of 2,3,7,8-tetramethoxythianthrene radical ion(1+) have been crystallized, and in each of these the heterocycle is planar [87ZN(B)169].

Radical anions can be produced upon one-electron reduction of thianthrene oxides, usually using potassium, but also using butyllithium (77OMR269) or polarography (73HCA196). These, too, have been subjected to ESR investigation (63JA1821; 65JPC2108, 65MI3). For example, thianthrene 5,5,10,10-tetroxide radical ion(1-) gave a five-line spectrum,

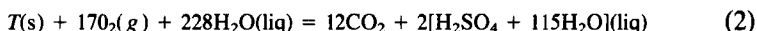
which seemingly (65JPC2108) implies coupling of the odd electron, as mentioned previously, with the 2-, 3-, 7-, and 8-protons, and by analogy, also implies some importance for contributors such as **19**. Study of the



radical ions(1-) from the tetroxides of 2,7-dimethyl- (nine lines) and 2,7-dichloro- (three lines) thianthrenes seems to confirm this interpretation (65MI3). However, three-line patterns for the radical anions derived from thianthrene 5-oxide and *trans*-, but not *cis*- (five lines) thianthrene 5,10-dioxides show the situation to be far from simple (65JPC2108).

H. MISCELLANEOUS PHYSICAL PROPERTIES

There appears to be no quantitative measurement of the pK_a of thianthrene, however, it is said to be completely protonated (presumably on sulfur) in anhydrous hydrogen fluoride (57JCP827). The vapor pressure over a range of 0.01–4.0 torr (81MI4) and between 430 and 593 K (83MI3) has been measured. The lattice energy of thianthrene, -24.7 ± 1.5 kcal mol⁻¹, was computed from an experimentally determined heat of sublimation of 23.3 ± 1.5 kcal mol⁻¹ (79JCP305); the molar enthalpy of vaporization was evaluated as 72.4 kJ mol⁻¹ at 435 K, and 67.3 kJ mol⁻¹ at 585 K (83MI3). Thianthrene is a recommended reference material for energy of combustion measurements (74PAC399); for the process shown in Eq. (2),



the enthalpy of combustion, $\Delta H^\circ C(25^\circ)$, is -7253.27 ± 1.40 kJ mol⁻¹ leading to values of enthalpy of formation $\Delta H_f^\circ(25^\circ)$, of 184.23 ± 1.50 , and 411.97 ± 0.12 kJ mol⁻¹ (66MI; 75MI3). Thianthrene has an exaltation rotation value E of $+973 \mu r$, and this was compared with a computed value (74BSF2379). The electrical conductivity of thianthrene, in the solid state and crystallized from ethanol, was in the range 10^{-3} – 10^{-5} Ω^{-1} cm⁻¹ over a temperature range 20–90°C. To account for the conduction, the authors suggested a “hopping” mechanism in which electrons hop from one sulfur to a sulfur in an adjacent molecule, calling attention to the close approach (3.78 Å) of sulfur atoms determined by X-ray measurement [76ZN(B)285]. The conductivity of thianthrene as a 2% solution in nitrobenzene was

$0.2\text{--}0.27 \times 10^8 \Omega^{-1} \text{cm}^{-1}$; this was slightly increased, as mercury(II) chloride complex, to $5.0\text{--}7.5 \times 10^8 \Omega^{-1} \text{cm}^{-1}$ [78CI(L)729]. Another study of crystalline thianthrene demonstrated electrical conductivity in response to irradiation. The direct current (dc) photoconductivity, excited between 300–400 nm, was shown to be proportional to light intensity to the 1.5 power; this was explained by interaction between singlet and triplet excitons. Pulsed photoconductivity of 385–440 nm depended on the square of the light intensity, and between 450–640 nm it followed a cubic dependency. In the former case, this was explained as carrier generation via photoionization of triplets, and in the latter case, as photoionization of 2-photon-produced singlet excitons (82JCP3768).

The first ionization potential of thianthrene was measured as 7.93 (81ZOB1293; 83ZOB2537) and 8.19 (eV) ([83JCS(P2)1109], by photoelectron spectroscopy (PES), and 7.8 eV by mass spectrometry (66MI2). These values have been compared with those available from computational methods [70BCJ3929; 81ZOB1293; 83JCS(P2)1109, 83ZOB2537]. Quantum mechanical treatment of bond and molecular polarizability gave a value of average molecular polarizability, α_M , of $277.682 (10^{-25} \text{cm}^3)$ for thianthrene (73JPC2552).

III. Reactivity

A. REACTIVITY OF RING ATOMS

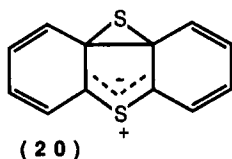
1. General Survey

Electrophilic substitution of thianthrene takes place at C-2. No examples of even minor amounts of 1-mono-substituted product have been reported. Disubstitution gives 2,7- (usually) or 2,8-products. In a few cases, 2,6-derivatives have been claimed. The presence of a sulfoxide or sulfone unit greatly reduces the susceptibility of either ring to electrophilic substitution. Carbon-centered electrophilic addition to sulfur to produce 5-*R*-thianthrenium salts has been described rarely; most examples of the formation of such salts have involved the thianthrene radical ion(1+). Treatment of thianthrene with alkyl/aryllithiums produces the 1-lithio-species, and these organometallic derivatives allow the introduction of substituents at this position.

A great deal of work has been carried out on the thianthrene radical ion(1+), which can be produced from thianthrene by a variety of one-electron oxidations. The radical cation reacts at sulfur with nucleophilic species, giving rise to 5-substituted products, oxides, ylids, and 5-*R*-thianthrenium salts.

2. Thermal and Photochemical Reactions Involving No Other Species

Thianthrene is one of the sulfur-containing compounds in coal and has therefore served as a model compound for experiments aimed at devising methods to remove sulfur-containing compounds from coal and other fuels, for the purpose of making fuels that produce less of the highly undesirable oxides of sulfur combustion products (see also Section III, A, 4). For example, heating thianthrene at 550°C leads to partial desulfurization, the main product being dibenzothiophene, which was highly resistant to further thermal degradation up to 950°C (68MI1). Plasma desulfurization gave dibenzothiophene quantitatively (80LA441). One may interpret [80AG(E)947] this process as a chelotropic elimination of sulfur from a thiocarbonyl ylid such as **20**.

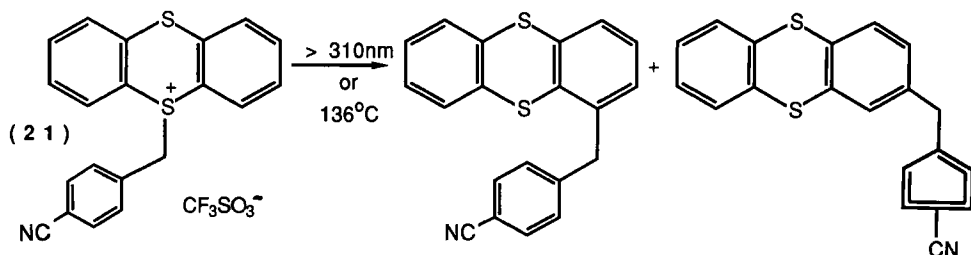


In a study of the carbonization (\rightarrow 525°C) and graphitization (\rightarrow 2500°C) of thianthrene in comparison with anthracene, it was shown that the carbons of the heterocycle are nongraphitable; between 1200°C and 2500°C, sulfur was evolved continuously (85MI3). Aluminum chloride catalytic carbonization of thianthrene has also been studied. At lower temperatures than without a catalyst, thianthrene produced an isotropic coke; catalytic co-carbonization with anthracene and 9,10-dihydroanthracene gave mosaic and needle cokes, respectively (80MI6, 80MI7). Poly(arylene sulfides) were shown to be produced by aluminum chloride treatment of thianthrene at 180–350°C (79URP659582).

In the context of the desirability of removing sulfur compounds from fuels, a bacterial strain has been identified that will metabolize thianthrene to water-soluble products under aerobic conditions (83MI5). A thermophilic organism, *Sulfolobus acidocaldarius*, removed 38% of the sulfur, as measured by sulfate release, in 4 weeks at 70°C (87MI2).

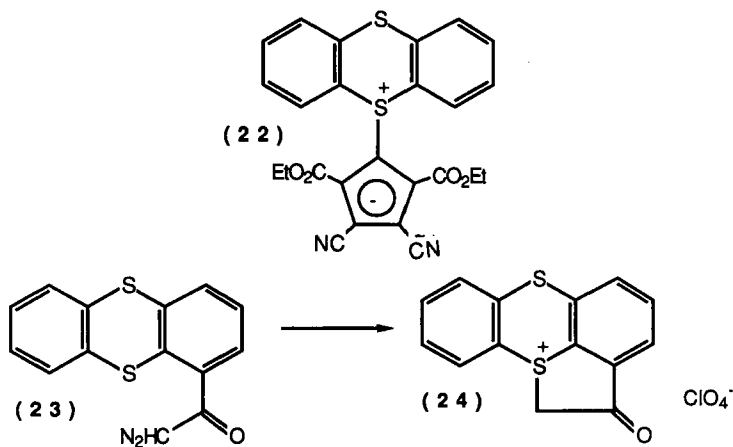
Irradiation of salt **21** gave a mixture of the 1- and 2-benzyl-substituted products, the former predominating by 7 : 1. Heating above 136°C gave the same products (ratio not reported). The rearrangement was rationalized as involving photochemical, or thermal, dissociation into 4-cyanobenzyl radical and the thianthrene radical ion(1+), the latter being detected spectroscopically in the thermal reaction. It was recognized however, that the regioselectivity observed for C-C recombination is at variance with spin

density pattern ($2 \gg 1$) identified by ESR spectroscopy of the thianthrene radical ion($1+$) (86T6123).

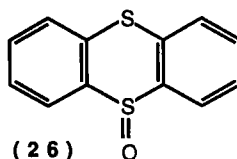
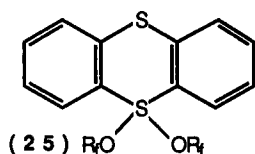


3. Electrophilic Attack

a. *At Sulfur.* Few examples of the formation of thianthrenium salts by direct alkylation or arylation of thianthrene have been recorded; thianthrene does not react, for example, with iodomethane at 100°C (1893LA218). 2-Aminothianthrene could be *N*-methylated without attack at sulfur (37JCS1592). This puts thianthrene in accordance with diphenyl sulfide, which requires Ag(I) catalysis to effect *S*-methylation (61CB2942). 5-(4-Cyanobenzyl)thianthrenium trifluoromethanesulfonate (triflate), **21**, was made by reaction with the benzyl chloride in the presence of silver triflate (86T6123); 5-phenylthianthrenium hexafluoroarsenate was made by arylation with diphenyliodonium hexafluoroarsenate in the presence of copper(II) benzoate at 120°C (80MI8); and the internal salt, **22**, was made by reaction with the phenyliodonio-cyclopentadienide in diglyme at 120°C (79CB1267). Decomposition of the diazomethyl ketone (**23**) in 60% perchloric acid at room temperature effected intramolecular alkylation at sulfur, yielding tetracycle **24**[80JCS(P1)1185].



Direct formation of 5,5-dihydro-5-iminothianthrene by reaction with hydroxylamine mesitylsulfonate presumably involves, first, electrophilic amination at sulfur (74TL1973). Electrophilic S-bromination (see also Section III, A, 3, b) must be presumed to initiate the conversion of thianthrene into the sulfurane **25** by reaction with bromine in the presence of the alcohol ($R_fOH = 1,1,1,3,3,3$ -hexafluoro-2-phenyl-2-propanol) (77JOC3222).

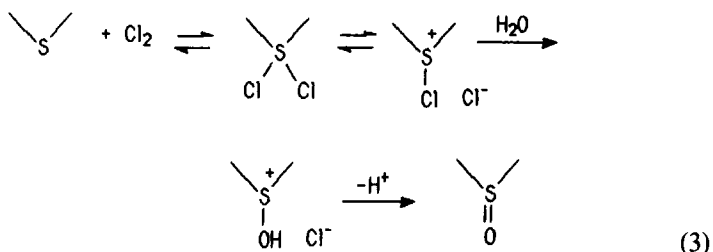


Early attempts to nitrate thianthrene showed S-oxidation to proceed more rapidly than C-nitration, both 5-mono- and 5,10-dioxides being available in this way. Production of these, and tri- and tetroxide formation, were already well-studied processes by 1960 (66HC1155).

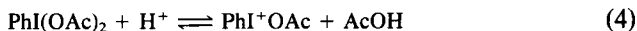
Most of the reactions of the thianthrene radical ion($1+$) produce at least some thianthrene 5-oxide (**26**) because of the ion's rapid, much studied (see following) reaction with (adventitious) water. The monoxide is produced efficiently from T^{++} by reaction both with sodium nitrite (72JOC2691) and nitrate (79JPC2696); anodic oxidation of thianthrene in aqueous acetic acid solution gave the monoxide quantitatively, again via the T^{++} and at higher voltages, further reaction produced all five further S-oxidation products (73MI1). A mixture of thianthrene 5-oxide and thianthrene resulted from treatment of T^{++} with potassium superoxide (80JA4526). *t*-Butyl hydroperoxide converts T^{++} into a mixture containing, in addition to the 5-oxide, thianthrene and the *cis*-5,10-dioxide; some 5-acetylthianthrenium perchlorate was also obtained (84MI1).

In practical terms, the 5-oxide can be produced by reacting with aqueous *N*-bromosuccinimide (63JAP439052), *N*-bromo- ϵ -caprolactam (74MI2), *N*-chloro-nylon-66 (72CL1023) [though another report states that the 5,10-dioxide is produced (77MI3)], chlorine in aqueous acetic acid [81JCS(P2)382], bromine in the presence of Troeger's base (78MI4), one molar equivalent of iodobenzene dichloride in aqueous pyridine [68JCS(C)659], aryldiazonium ions, in which the aromatic ring carries an electron-withdrawing substituent (56JA2163), and a methylene chloride solution of 1-acetyltriazo[4,5-*b*]pyridine in a two-phase system with aqueous hydrogen peroxide (87SC515). Thianthrene 5-oxide is also efficiently produced by reaction of thianthrene with ozone (78JOC675; 84BCJ2526). Dinitrogen tetroxide converts thianthrene into monoxides or 5,10-dioxides (55; 45, *cis* : *trans*) (65MI1).

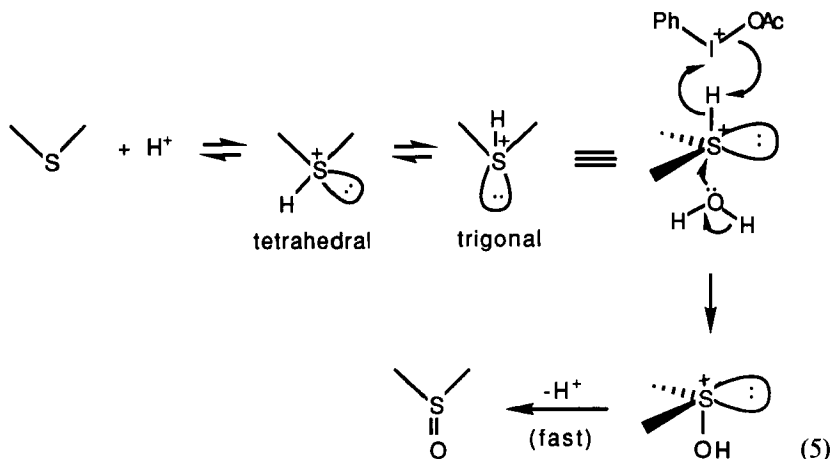
Thianthrene 5-oxide is neatly used as a probe for the electrophilic–nucleophilic character of oxidants (84JA5020; 86AG85, 86AG185; 87JOC2800; 88JOC1078). Electrophilic agents tend to attack at the sulfide sulfur, producing 5,10-dioxide, whereas oxidants with nucleophilic character, for example potassium superoxide in the presence of 18-crown-6 (81BCJ2712) attack at the sulfoxide-sulfur, generating the 5,5-dioxide. In contrast, chlorine in acetic acid converts thianthrene 5-oxide only into the 5,10-dioxide (16:1, *cis*:*trans*); *S*-oxidation was interpreted by the sequence shown in Eq. (3) [81JCS(P2)382].



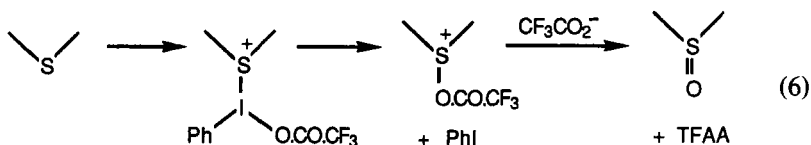
Relative rates of sulfide-*S*-oxidation for thianthrene, its 5-oxide, and its 5,5-dioxide were $6.5 \times 10^4 : 2.6 \times 10^3 : 1$. For the comparable iodobenzene diacetate conversion of thianthrene 5-oxide into the 5,10-dioxide (8:1, *cis*:*trans*), a mechanism shown in Eqs. (4) and (5) involving rehybri-



dization at sulfur was suggested [81JCS(P2)382], though no specific consideration was given to the stereochemical implications of this sequence in the thianthrene ring context.



Oxidation of thianthrene with 2 mol equivalents of iodobenzene dichloride in aqueous pyridine gave 100% of the *cis*-5,10-dioxide; oxidation with *t*-butyl hypochlorite in methanol or bromine in the presence of diazabicyclooctane also gave *cis*-dioxide exclusively [68JCS(C)659]. The *trans*-isomer can be obtained with high efficiency by oxidation with an excess of iodobenzene bis(trifluoroacetate); the sequence suggested in this case involves formation of trifluoroacetic anhydride (TFAA) as a final byproduct, as shown in Eq. (6) [85JCR(M)2201, 85JCR(S)186]. Ozone also



oxidizes thianthrene 5-oxide, to a 77:3 mixture of *trans*- and *cis*-5,10-dioxides (84BCJ2526). Iodobenzene dichloride produced a mixture of the *cis*- and *trans*-5,10-dioxides upon reaction with 7-nitrothianthrene-1-carboxylic acid (71RC107). Heating *trans*-thianthrene 5,10-dioxide above its melting point gives an equilibrium mixture of *cis*- and *trans*-isomers in which the *cis*-isomer is predominant (11CB756).

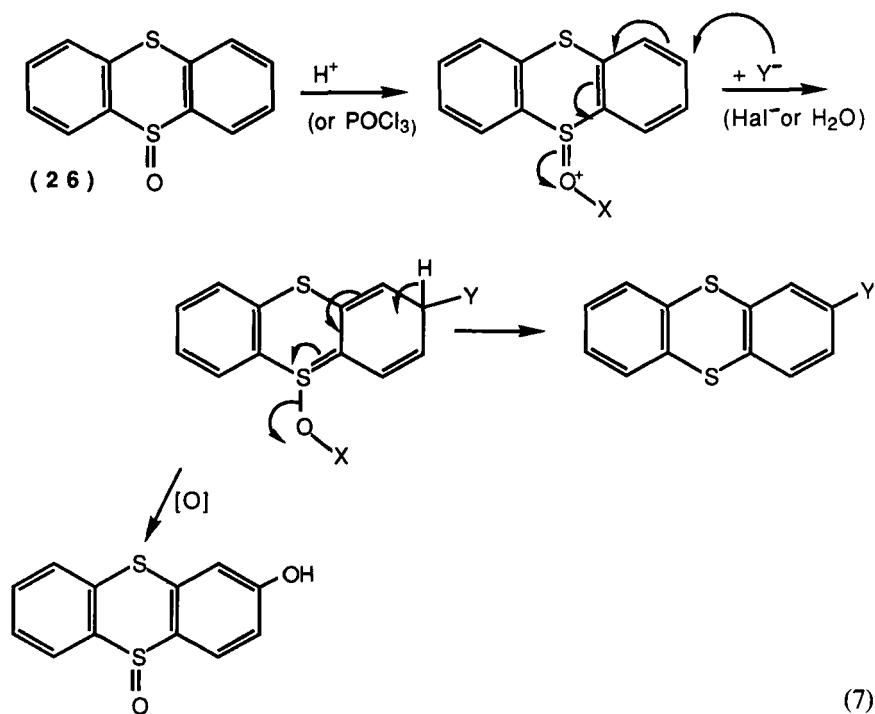
Chlorine in hot acetic acid converts thianthrene into 5,5,10-trioxide efficiently (55JA5944). Hydrogen peroxide can be used to produce 5,10-dioxides from thianthrene or from halo-, alkyl-, methoxycarbonyl- (62MI2; 64JA2957), nitro- (71RC107), or carboxyl-substituted (61RC745) thianthrenes, but used in excess and for longer periods, the reagent will produce tetroxides from thianthrene itself or from the 5,10-dioxide (62MI2; 66RC1243; 67JA4815). The use of hydrogen peroxide or *t*-butyl hydroperoxide in the presence of molybdenum(V) chloride or molybdenum hexacarbonyl for the *S*-oxidation of thianthrene has been studied (72IZV2744). Thianthrene or thianthrene 5-oxide were reported to be oxidized photochemically to afford benzene 1,2-disulfonic acid (83MI4).

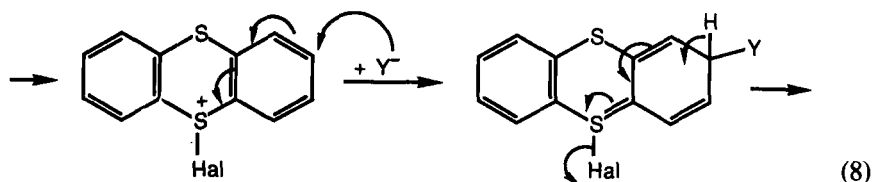
b. *At Carbon*. Monoacetylation of thianthrene at C-2 has been described many times (61RC745; 62MI1; 66RC1021; 70JMC620; 73BSF1460); a combination of acetyl chloride and aluminum chloride in carbon disulfide as solvent is the most common used. 2,7-Diacetylation (62MI3; 73BSF1460; 79MI3; 87MI3, 87MI6) can also be effected efficiently; the orientation has been confirmed by X-ray analysis (quoted in 87MI6). These two acetylation products provide the main entry to 2- and 2,7-dicarbon-substituted thianthrenes. Friedel-Crafts 2-bromacetylation, -benzoylation, -phthaloylation (11CB1233; 73BSF1460),

-2-hydroxyphenyloxyformylation (67MI1), 3-chloropropanoylation (60MI1), and reaction with succinic anhydride (50USP2480220; 88MI5) have also been described. Polymer ketones, formed by reacting thianthrene with iso- and terephthaloyl, adipoyl chlorides, in the presence of AlCl_3 /polyphosphoric acid (PPA) (82MI7), pyromellitic anhydride, catalyzed by ZnCl_2 at 450°C (84MI6), or polyisocyanate [84JAP(K)58129017] are probably linked 2,7-with respect to the thianthrene nuclei.

Mono-2-alkylation of thianthrene with 2-chloropropanoic acid (74GEP2245940) and dialkylation with phenyltrichloromethane/ AlCl_3 (81EGP143901) have been claimed in the patent literature. The unusual 2,6-substitution pattern is claimed for chloromethoxymethylation using $\text{ClCH}_2\text{OMe}/\text{SnCl}_4$ (76IZV2799).

Exhaustive chlorination of thianthrene yields a mixture of polychloro-derivatives, the main component being 2,3,7,8-tetrachlorothianthrene (77USP3989715). In a survey, authors looking for dioxinlike activity in sediment from a sanitary sewer near a chemical factory detected tetrachlorothianthrene using gas-liquid chromatography and mass spectrometry (85MI4).





In order to achieve C-halogenation, one must avoid hydrolysis of initially formed S^+ -halide, which produces *S*-oxide (see earlier). 5,5-Dihydro-5,5-dichlorothianthrene is converted into 2-chlorothianthrene when allowed to stand (11LA312). Bromination in nitrobenzene gives a mixture of 2,7- and 2,8-dibromothianthrenes (55JA5944; 58JOC313); a patent claims formation of 2,7- (64USP3106563). Bromination in hot acetic acid produces 2,3,7,8-tetrabromothianthrene (58JOC313).

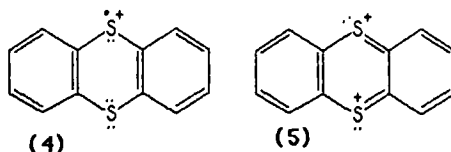
Based on analogy with reductive halogenation, which involves treatment of thianthrene 5-oxide (**26**) with hydrochloric or hydrobromic acids to produce some 2-halothianthrene (55JA5944; 65JOC2145) [phosphorus oxychloride has a comparable effect (68JCS(C)1230)], it can be suggested (63JOC2828) that electrophilic substitution in these cases could actually involve addition of *nucleophilic* halide at C-2 in a thianthrenium salt or sulfoxide⁺-OX species, as shown in Eqs. (7) and (8). The isolation of 2- or 3-hydroxythianthrene 5-oxide, after adding a *c.* H_2SO_4 solution of the heterocycle to ice, may represent oxidative trapping of just such an adduct (63JOC2828). The conversion of thianthrene 5,10,10-trioxide into the 5,5-dioxide using hot HBr, i.e., without ring bromination, seems to be inconsistent with the concept of Br^- addition (55JA5944). Conventional electrophilic substitution at C-2 cannot be discounted, and indeed this regiochemistry has been rationalized as an electrophilic-substitution process by examining the highest occupied molecular orbitals (HOMOs) in thianthrene (86T3707).

Treatment of thianthrene with $S/AlCl_3$ at only 80°C gives polymeric materials of the form in **12** (Section II,D), the formation of which probably involves electrophilic attack by sulfur catalyzed by the Lewis acid (85MI2; 88MI3).

Nitration (at C-2 and C-4) and diazocoupling (C-4) of 1-hydroxythianthrene occur in the activated aromatic ring, in the former case with *S*-oxidation (57JA991).

c. One-and Two-electron Oxidations: Thianthrene Radical Ion(1+) and Thianthrenediium. The oxidative removal of an electron from a sulfur in thianthrene produces thianthrene radical ion(1+), $T^{\cdot+}$ (**4**). A second one-

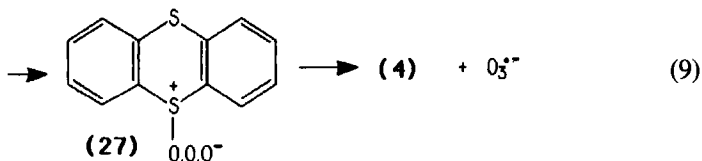
electron oxidation gives rise to the doubly positively charged thianthrene-dium ion, T^{2+} (5). The much studied formation and chemistry of this



radical cation and the less studied formation of thianthrenediiums will be discussed in this section.

i. *Oxidation of thianthrene to thianthrene radical ion(1+)*. The formation of T^{+} itself was first noted in *c.* H_2SO_4 solution, sulfur dioxide being the sulfuric acid reduction product (62JA4798, 62JCS4963). This medium has been used to study a large range of substituted thianthrene radical ions(1+) (64JOC21; 78LA785). Much of the fine details of this and other chemical oxidations still remain unresolved. Reaction of thianthrene with aluminum chloride in benzene, chloroform, or nitromethane also produces T^{+} in solution (62JA4798). When aluminum chloride in nitromethane was employed, it was speculated that the solvent may be the oxidant. When thianthrene was put in contact with heavy metal halides in the solid state, a very stable ESR signal was demonstrated, corresponding, however, to $\leq 6\%$ of the total heterocycle present; the spin concentration increased with temperature and with applied pressure (74CC74). In a similar study using Al_2O_3/MoO_3 , the thianthrene was absorbed from benzene solution into the catalyst as it cooled from activation at $500^\circ C$, thus generating T^{+} and reduced $Mo(V)$ (75MI1; 80JPC1020).

Thianthrene radical ion(1+) is generated upon treatment of the heterocycle with ozone; an assumed initial adduct (27) is thought to dissociate (78JOC675) (Eq. 9). When haloazoxybenzenes are decomposed with sul-



furic acid, the intermediacy of a radical cation was demonstrated by electron transfer from added thianthrene, hence, the spectroscopic characterization of T^{+} (82BCJ546). Irradiation in the presence of *p*-benzoquinone in TFA solution also gives T^{+} by electron transfer to the benzoquinone radical cation (83JA2480, 83MI8). Similarly, 2,3-dichloro-

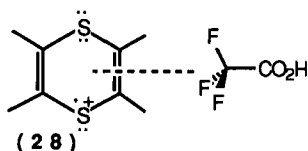
5,6-dicyano-*p*-benzoquinone (DDQ), in the presence of a trace of TFA, produced a solution containing $T^{\cdot+}$ (86MI1). Apart from sulfuric acid and aluminum chloride oxidations, other practicable means for the chemical production of solutions of $T^{\cdot+}$ are oxidation with 4-chloro-1-hydroxy-2,2,6,6-tetramethylpiperidine nitroxide in the presence of TFA (85TL4201), chlorine dioxide (85TL1765), and treatment with methanesulfonic acid in nitrobenzene, the oxidant being either the nitrobenzene or atmospheric oxygen (66JPC2064). Thianthrene is also converted into $T^{\cdot+}$ by oxidation with nitrosyl borofluoride. Although early attempts to isolate a solid $T^{\cdot+}BF_4^-$ salt were unsuccessful (77JOC561), recently (88JOC5142), and very significantly from the viewpoint of those wishing to study the chemistry of $T^{\cdot+}$, brown, solid $T^{\cdot+}BF_4^-$ has been obtained in quantities of up to 5 g. It was shown to be stable in MeCN solution for weeks. The dark blue solution, obtained by treating thianthrene with $NO^+BF_4^-$ in acetonitrile, was mixed with dry ether when the solid salt precipitated and could be filtered.

A brownish-purple solid salt, $T^{\cdot+} SbCl_6^-$, made by reacting thianthrene with antimony(V) chloride at room temperature in chloroform (62BCJ1137, 62JCS4963; 67BCJ2539), was shown, by comparison with a methylene chloride solution of the salt, to have the radical as free in the solid as in solution (69BCJ548). Antimony(V) chloride was used to oxidize a thianthrene-containing polymer, $-[T-C(Ph)=C(Ph)]_n-$, presumably at (? some of the) sulfurs, generating thianthrene radical ion(1+) units. This increased the conductivity of the polymer by a factor of 15 (86ZC74). The black crystalline solid, resulting from reaction of thianthrene with excess iodine chloride, has the composition $T^{\cdot+} Cl_3I_2^-$ and was stable at room temperature over weeks (69JOC3368). Solid salts were also obtained by oxidation of thianthrene with peracetic acid in the presence of hexafluoroantimonic acid to give $T^{\cdot+} SbCl_6^-$, and in the presence of tetrafluoroboric acid and tetraethylammonium bis(maleonitriledithiolate)nickelate, $T^{\cdot+} Ni(mnt)_2^-$ was produced (75IC2357). Solid perchlorate and sulfate salts of 2,3,7,8-tetramethoxythianthrene radical ion(1+) have been known for some time (29LA162), and more recently, the crystalline $SbCl_6^-$ and I_3^- salts were obtained by oxidations using nitrosyl hexachloroantimonate and iodine, respectively [87ZN(B)169].

The solid $T^{\cdot+}$ salt which has been used in nearly all chemical studies is the EXPLOSIVE dark-reddish thianthrene radical ion(1+) perchlorate; *use of the salt in quantities greater than 50 mg is not advised* (62JCS4963; 69JOC3368). The salt is formed in 90% yield upon treatment of thianthrene with acetic anhydride/perchloric acid in carbon tetrachloride, at room temperature overnight.

Most of the mechanistic studies of the reactions of $T^{\cdot+}$ have been

achieved in electrochemical experiments (64JOC21). The radical cation has been electro-generated in sulfur dioxide at -40°C in the presence of $\text{Et}_4\text{N}^+ \text{BF}_4^-$, under which conditions the radical is stable, even to water (see later), on the coulometric time scale (79JA2316; 82MI6), at room temperature, in melts of 1-alkylpyridinium chloride/ AlCl_3 (1 : 2) (81MI2), and in an $\text{AlCl}_3/\text{NaCl}$ melt at 156°C (73MI3). At room temperature, solvents TFA or HClO_4 (72CC156), propylene carbonate with small percentages of TFA and TFAA (77MI2), but most often, nitromethane or acetonitrile, again in the presence of small percentages of TFA and/or TFAA, have been used (77CJC766). Solvents must be thoroughly pre-dried; the TFAA serves to scavenge final traces of water (73MI2; 75JA101). The use of aluminum oxide has been recommended in this last context (73MI2; 75JA101). Up to 10% of water can be added to TFA without affecting the reversibility of the cyclic voltamogram: This means that $\text{T}^{\cdot+}$ does not react with water (on this time scale) in 90% TFA (72CC156). Strangely, though, it does react with acetonitrile. This special role noted (72CC156) for TFA stabilization of $\text{T}^{\cdot+}$ has been rationalized by a specific interaction between the polarized trifluoromethyl group and the positively charged thianthrene central ring, as shown in **28**. In support of this idea, it was found that the disappearance of radical signal was faster in the presence of di- and monofluoroacetic acids (83MI8). In this context, it was found that adsorption of $\text{T}^{\cdot+}$ onto Amberlyte 15 does not convey stability, as was found for the phenothiazine radical ion(1+), perhaps simply because $\text{T}^{\cdot+}$ does not have a basic center (84MI5).



The crystalline SbCl_6^- and I_3^- salts of the radical ion(1+) from 2,3,7,8-tetramethoxythianthrene were obtained by oxidations using nitrosyl hexachloroantimonate and iodine, respectively (87ZN(B)169).

Thianthrene 5-oxide is converted, in concentrated sulfuric acid, into a solution of $\text{T}^{\cdot+}$ (62JA4798); sulfuric or perchloric acid in nitromethane can also be used (63TL993). One view is that this transformation involves homolysis of the *O*-protonated sulfoxide, with hydroxyl radical as byproduct, though the involvement of a dication has also been suggested (63JOC2828).

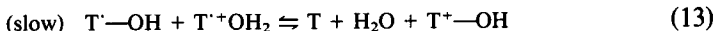
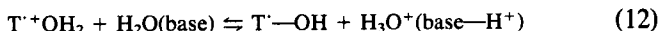
In solvents that are sufficiently inert (dry) (cf. 73MI2; 77JOC976; 77MI2), the electrochemical oxidations of thianthrene to thianthrene radical ion(1+), $\text{T}^{\cdot+}$, and then, further, to thianthrenediiium, T^{2+} , are revers-

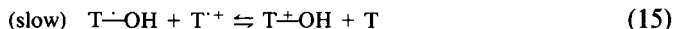
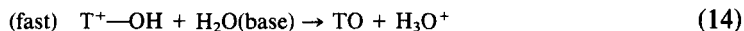
ible on the voltametric time scale. Values for the half-wave potentials, E_1 , and E_2 , variously determined, are (respectively) 0.865, 1.19 (in MeCN) (66BSF2510); 0.64, 0.90 (CH_2Cl_2 at -70°C) (72TL2419); 1.25, 1.65 (MeCN) (77JOC976); 0.91 (MeCN) (86MI4); 0.925, 1.67 ($\text{AlCl}_3/\text{NaCl}$ at 140°C) (73MI3); 0.99, 1.98 [$\text{SO}_2(\text{liq})$ at -40°C] (79JA2316); 0.53, 0.88 (MeCN/1% TFAA) (77CJC766); 0.96, 1.31 (MeCN) (70ZC147); 1.26, 1.77 (75JA101); 0.84, 1.29 (propylene carbonate/1% TFA/3% TFAA; the dication persists for several seconds in this solvent mixture); 1.021 (MeCN), 1.063 (DMF), 1.042 (propylene carbonate), and 1.083 (CH_2Cl_2) [84ACS(B)759]. Values of 0.54 and 0.79 (MeCN/ Bu_4N^+ and ClO_4^-) were determined for 2,3,7,8-tetramethoxythianthrene [73JA2375; 85ZN(B)774], though later measurements gave 0.98, 1.37 (CH_2Cl_2), and 0.86, 1.21 (MeCN) for 2,3,7,8-bismethylenedioxythianthrene; 1.10, 1.51 and 1.01, 1.33 in the same pair of solvents were found, and values of 1.01, 1.29 (MeCN) were quoted for 2,3,7,8-bisethylenedioxythianthrene [88JCS(P1)2095]. The entropy for formation of T^{++} in various solvents was determined from electrochemical measurements and lies in the range 14.5–31.2 cal/kmol [84ACS(B)759].

ii. *Reactions of thianthrene radical ion(1+) and thianthrenediiium with water; conversions to thianthrene 5-oxide.* When thianthrene radical ion(1+) reacts with water, thianthrene 5-oxide (designated TO in kinetic Eqs. below) and thianthrene are produced; the use of ^{18}O -labeled water gave ^{18}O -labeled thianthrene 5-oxide (66TL1591). That this apparently simple process is in fact complex was first recognized when it was shown to be second order in T^{++} (69JA1872, 69JOC3368), which led to the view that a disproportionation [Eq.(10)]

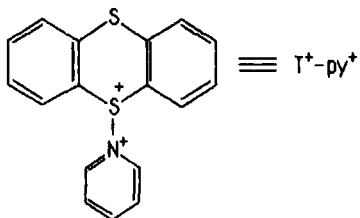
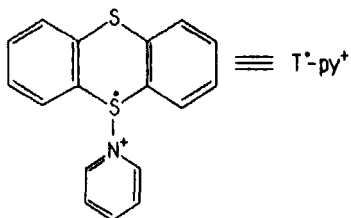
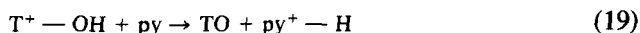
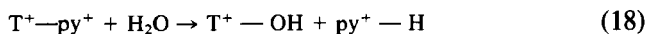
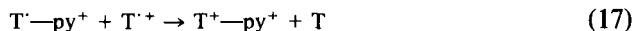


was followed by reaction of the dication with water. Later however, electrochemical measurements showed that the equilibrium would produce so little dication [in MeCN (T^{++}) $\sim 10^6(\text{T}^{2+})$ (70JA7488)], that this hypothesis is untenable [72MI1; 73JCS(P2)1594; 75JCS(P2)755; 79JA2316; 80JPC2557]. Further kinetic studies showed the rate to depend on water concentration, the order varying from 1 to 3 (77JOC976; 84MI2), and pH [82ACS(B)421]. An appropriate kinetic scheme that accommodates these data is shown as Eqs. (11)–(14); a variant is shown in Eq. (15).

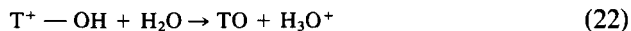
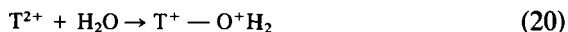




Cyclic voltammetry of thianthrene in the presence of two molar equivalents of pyridine generates thianthrene 5-oxide and not T^{2+} . Having shown 2-(pyridinium-1-yl)thianthrene to have half wave potentials, 1.45 and 1.74, different from those of thianthrene, the kinetic scheme summarized by Eqs. (16)–(19) was proposed (77JOC976).

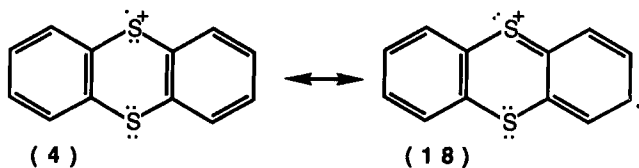


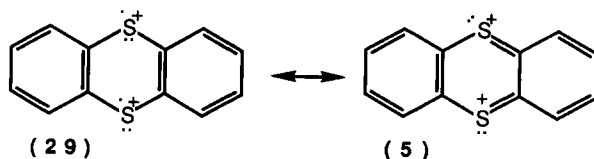
The prediction that thianthrenediium would react with water to give the 5-oxide was vindicated by a study conducted at -40°C in liquid sulfur dioxide, which showed that while T^{2+} did not react on the coulometric time scale with water (or anisole) at that temperature, thus providing a means for generating stable solutions of T^{2+} , the T^{2+} produced by a second oxidation *did* react with water to give thianthrene 5-oxide. T^{2+} also reacted with anisole, presumably giving 5-(4-methoxyphenyl)thianthrenium ion. The water reaction was first-order in water and the dication, leading to a kinetic scheme summarized in Eqs. (20)–(22) (82MI6).



iii. *Generation of thianthrenediium, T^{2+} .* Irradiation during cyclic voltammetric experiments conducted in dimethylformamide (DMF) caused an increase in anodic peak height and a diminishment of the cathodic peak on the reverse scan, which may have been caused by formation of

T^{2+} [78ACS(B)505]. A deep-red solution of thianthrenediium was generated electrochemically in SO_2 (liq); it was stable for ~ 2 hrs (79JA2316). A green solution of 2,3,7,8-tetramethoxythianthrene radical ion(1+) produced in *c.* sulfuric acid was converted into a blue colored solution of the tetramethoxythianthrenediium dication by warming (78LA785). A blue solution of this dication was also obtained by passing oxygen into a nitromethane solution containing $AlCl_3$, and the dark blue, crystalline dip-erchlorate was produced by oxidation with perchloric acid (78JA2375; 76JPC988). Colored solids were produced by reactions of 2,3,7,8-tetramethoxythianthrene with iodobenzene dichloride in chloroform in the presence of HCl (\rightarrow dark green solid $[C_{16}H_{16}O_4S_2^{+}Cl^{-}HCl]$) and in acetic acid (\rightarrow intense blue $[C_{16}H_{16}O_4S_2^{2+}]2Cl^{-}.4AcOH$). Both solids gave a mixture of the tetramethoxythianthrene 5-oxide and the tetramethoxythianthrene upon addition to water. The solid materials, then, were considered to contain radical cation and a mixture of dication and the thianthrene, respectively (78LA785). The apparant coexistence of dication and the corresponding thianthrene must be contrasted with the report that it was possible to titrate 2,3,7,8-tetramethoxythianthrenediium with the corresponding tetramethoxythianthrene in nitromethane in the presence of $MgClO_4$, apparantly producing tetramethoxythianthrene radical ion(1+) (73JA2375). By studying the photo-generated triplet ESR spectra of thianthrene and 2,3,7,8-tetramethoxythianthrene and the tetramethoxythianthrenediium, at $-96^{\circ}C$ in solid nitromethane, it was concluded that tetramethoxythianthrenediium is a ground-state triplet. Hückel molecular orbital calculations, however, seem to show that the energy-level separation between the two highest-energy bonding orbitals is too large for the dication to be a ground-state triplet. Clearly, calculations need assumptions as to the planarity of the species involved, and the discrepancy may reflect actual conformational changes between tetramethoxythianthrene radical ion(1+) and the corresponding thianthrenediium, i.e., it could possibly have bearing on the flatness of the two charged species. Resonance contributors **18** and **5** for $T^{\cdot+}$ and T^{2+} , respectively, imply planarity (76JPC988) (**4** and **18**; **29** and **5**). Early MO calculations concluded that $T^{\cdot+}$ is probably not planar (63TCA397; 65MI2), a view that seemingly received confirmation from the magnitude of calculated energy barriers to flipping -6 kcal mol $^{-1}$ for $T^{\cdot+}$ and 4–10 for excited $T^{\cdot+*}$. Fold angles of 130° were



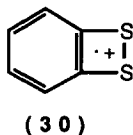


evaluated (86T3707). However, X-ray crystallography has recently shown that in two salts of 2,3,7,8-tetramethoxythianthrene radical ion(1+), the heterocyclic radical cation is *planar* [87ZN(B)169].

iv. *Photochemical and thermal reactions of thianthrene radical ion(1+)*. The fluorescence spectrum of $T^{\cdot+}$ has a maximum at 580 nm [83ACS(B)459; 84JA5083], which can be quenched by radical anions [83ACS(B)459]. Several studies of electrogenerated chemiluminescence have described using thianthrene/PPD (2,5-diphenyl-1,3,4-oxadiazole)/ $S_2O_8^{2-}$ (84MI4) and T/PPD (72JA1522; 74JA1243; 75AC249, 75JA1274; 77JA7754), the light being emitted from $^1T^*$. From the most recent study the scheme proposed is described by Eqs. (23)–(25).



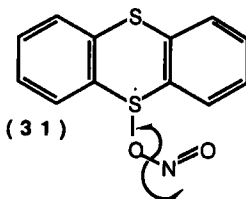
Irradiation of $T^{\cdot+}$ perchlorate in acetonitrile gave a C-substituted cyanomethylthianthrene (80MI1). Warming a solution of $T^{\cdot+}$ in methylene chloride, in the presence of aluminium chloride, to room temperature, and then remeasuring the ESR spectrum showed a second signal, downfield of that of $T^{\cdot+}$, at a g value of 2.015, corresponding to benzodithiete radical ion(1+) (30). No mechanism for this extraordinary change was proposed (82CB2548).



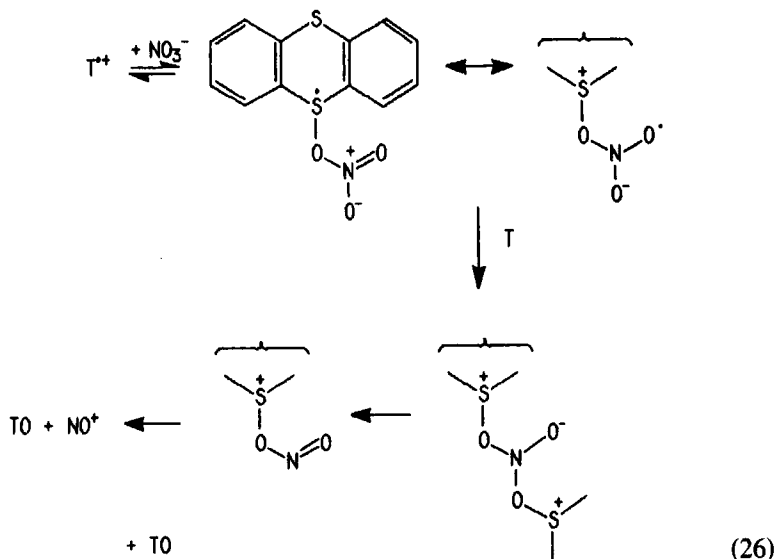
v. *Reactions of thianthrene radical ion(1+) with nucleophiles*. As discussed previously, thianthrene radical ion(1+) reacts rapidly with water, giving thianthrene and its 5-oxide. So from most reactions that have been described, these two products are also isolated, resulting from reaction

with adventitious water. For simplicity, in the remainder of this section, mention of the presence of thianthrene 5-oxide in product mixtures is omitted; when thianthrene itself is a product of the reaction in question, it is specified.

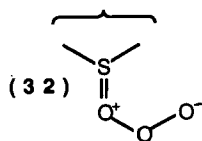
Oxidation of T^{++} to generate thianthrene 5-oxide occurs cleanly with nitrite and nitrate (72JOC2691). Incorporation of ^{18}O from labeled nitrite was considered consistent with a process (arrows on **31**) involving **31** as an intermediate and producing NO as byproduct.



Kinetic measurements on the nitrate reaction showed a second-order in T^{++} and a first-order dependance on nitrate, and thus a sequence that can be explained by Eqs. (26) and (27).

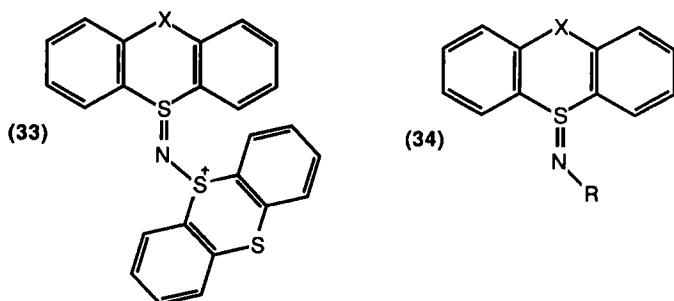


Interaction of T^{++} with potassium superoxide in acetonitrile generates a sulfinyl oxide (**32**), which then breaks down to give thianthrene, its 5-oxide, and oxygen in equal amounts. In experiments with added diaryl-

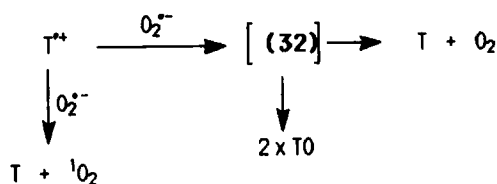


sulfides, it was shown that the sulfinyl oxide is an electrophilic oxidant, with regard to the diarylsulfide. Observation of the luminescence spectrum of $^1\text{O}_2$ showed its production during the process, and the workers deduced Scheme 1 to rationalize the data (80JA4526). A mixture of thianthrene, the 5-oxide, and the 5,10-dioxide resulted from exposure of $\text{T}^{+\cdot}$ to azobisisobutyronitrile (AIBN) (77MI1) or *t*-butylhydroperoxide (84MI1).

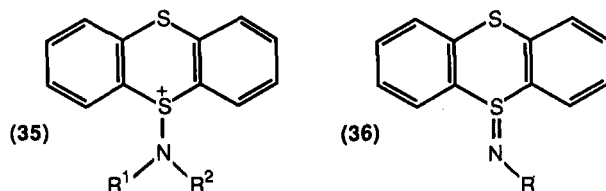
Thianthrene radical ion(1+) reacts with ammonia to produce salt **33** ($\text{X} = \text{S}$), alkaline hydrolysis of which afforded the sulfimine **34** ($\text{X} = \text{S}$, $\text{R} = \text{H}$) and thianthrene 5-oxide. The sulfimine was unstable in light, and hydrolyzed to the corresponding oxide by aqueous acid, but gave a stable *N*-tosyl derivative (**34**) ($\text{X} = \text{S}$, $\text{R} = \text{Ts}$) (72JA1026).



The phenoxathiin sulfimine (**34**) ($\text{X} = \text{O}$, $\text{R} = \text{H}$) reacted with $\text{T}^{+\cdot}$ to give a mixed system salt **33** ($\text{X} = \text{O}$) (75JOC2756). Extending these findings to primary amines produced a range of S^+ -alkylamino salts (**36**) ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$, *Et*, *n*-*Pr*, C_6H_{11} , *t*-*Bu*, PhCH_2) (74JOC2537; 77JOC561, 77JOC1538), alkali treatment of which released the corresponding neutral sulfimines,



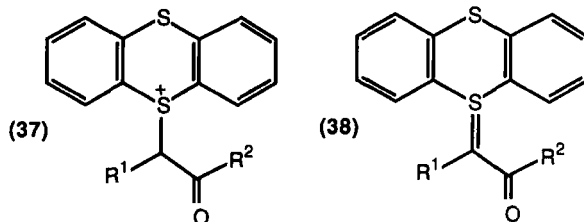
SCHEME 1



36, and to secondary amines, the salts **35** ($R^1 = \text{Me}$, $R^2 = \text{Me}$, $n\text{-Pr}$, C_6H_{11} , PhCH_2 , and $R^1 + R^2 = \text{carbazole}$) (74JOC2537; 77JOC1538). It was shown that the sulfinimes could be methylated on nitrogen under mild conditions to generate *N,N*-dialkylated salts **35** (77JOC1538). Primary aryl- (and methyl)-sulfonamides also react with T^{+} at nitrogen, yielding thianthrene *N*-arylsulfonylsulfinimes (**36**) ($R = \text{SO}_2\text{R}'$) directly (84MI1) and salts **35** ($R^1 = \text{H}$, $R^2 = \text{N(H)SO}_2\text{Ar}$). However, *N*-aryl arylsulfonamides form 5-aryltianthrenium salts by attack para to the nitrogen (see later) (81MI9); the formation of rather complex product mixtures was explained by postulating the intervention of sulfonamidyl radicals (88MI1).

A quite different mode of reaction was observed for the reactions between thianthrene radical ion(1+) and the heterocyclic bases pyridine (72JOC2691) and 2,3-diazabicyclo[2,2,2]oct-2-ene (88JA7880); thianthren-2-yl- N^+ salts were obtained in each case. It was shown that 2 mol equivalents of the radical cation are required, the byproduct being thianthrene.

S-Alkylation and alkenylation can be achieved from reactions of T^{+} with ketones, alkenes, and alkynes; thus, the keto-thianthreniums **37** ($R^1 = \text{H}$, $R^2 = \text{Me}$, $t\text{-Bu}$, Ph , naphth-2-yl), together with thianthrene, were formed as their perchlorate salts (75JOC3857) from treatment with the methyl ketones. Indanone and 4-*t*-butylcyclohexanone formed comparable salts. Triethylamine treatment allowed the formation of ylids, e.g., **38** ($R^1 = \text{H}$, $R^2 = t\text{-Bu}$, naphth-2-yl). The positively charged thianthrenium unit in salts **37** acted in the role of leaving group, in favorable cases, being displaceable by attack at $\text{C}-\text{S}^+$ with arylsulfinate and xanthates as nucleophiles (75JOC3857).

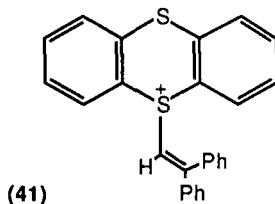
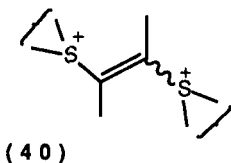
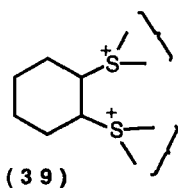


Ethyl acetoacetate reacted to give salt **37** ($R^1 = \text{EtO}_2\text{C}$, $R^2 = \text{Me}$), the free ylid **38** ($R^1 = \text{EtO}_2\text{C}$, $R^2 = \text{Me}$) again was produced by exposure to

triethylamine; reaction with cyanoacetamide produced an ylid (**38**) ($R^1 = \text{CN}$, $R^2 = \text{NH}_2$) directly.

Attempted displacement of thianthrene from **37** ($R^1 = \text{EtO}_2\text{C}$, $R^2 = \text{Me}$), using sodium 4-methylbenzenesulfinate, caused deacetylation to yield ylid **38** ($R^1 = \text{H}$, $R^2 = \text{OEt}$). It was shown that this was C-protonated to afford the thianthrenium salt **37** ($R^1 = \text{H}$, $R^2 = \text{OEt}$) upon treatment with acid.

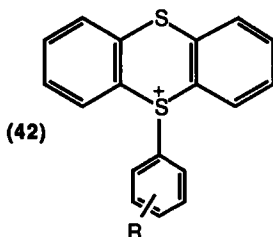
Cyclohexene (81JOC271; 84MI5) reacted with T^{++} in acetonitrile to give the bis-thianthrenium perchlorate **39**. Some success was achieved in displacing the thianthrene with nucleophiles such as cyanide and iodide, but elimination was a complication: the results were consistent with there being a trans relationship of the two thianthrenium rings with respect to the cyclohexane ring. Treatment of salt **39** with PhS^- produced thianthrene, quantitatively, together with cyclohexene (81JOC271). Thianthrene radical ion(1+) generated electrochemically in the presence of 1,1-diphenylethene produced salt **41**, in which it seemed a substitution had occurred. Displacements of thianthrene from the alkene (!) carbon in this salt were apparently achieved using xanthate and dimethyldithiocarbamate nucleophiles (81MI1).



Addition of 2 mol equivalents of T^{++} to alkynes gave bis-perchlorates **40** [$R^1 = \text{H}$, Me, Ph; $R^1 = R^2 = \text{MeO}$ (geometry not established)], which were explosive upon heating. The alkyne reactions were much slower than those with alkenes, and no reaction at all occurred with ethyl propiolate, from which it was concluded that all these reactions have the character of electrophilic addition to the unsaturated unit (79JOC915).

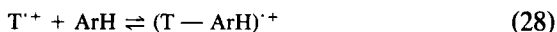
The synthesis of S^+ -arylthianthreniums by reaction of thianthrene radical ion(1+) with an aromatic compound has been thoroughly studied; thianthrene and a mol equivalent of perchloric acid are byproducts. Thus, acetanilide, phenol, *o*-chlorophenol, *o*-*t*-butylphenol, anisole, and (less efficiently because of competition from an electron-transfer process) *N,N*-dimethylaniline (71JOC2923) and *N*-aryl arylsulfonamides (81MI9), all give salts **42**. Attack is assumed to occur para to the electron-releasing substituent. 5-(Thianthrenium-2-yl)thianthrene perchlorate results from the reaction of thianthrene with $\text{T}^{++} \text{ClO}_4^-$ (83MI1).

Initial studies showed phenol to react faster than acetanilide, which, in turn, reacts faster than anisole (71JOC2923). Later, a value of 10^2 – 10^5 for

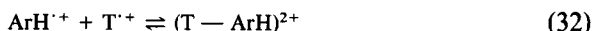


the relative reactivity of phenol–anisole was demonstrated (76JA997). In acetonitrile, the process was second-order in T^{++} (71JOC2923; 74JOC2534) and, as in the reaction with water, this was initially interpreted as the diproportionation Eq. (10), the thianthrenediiium ion thus produced being considered the species attacked by the aromatic. Later it was demonstrated that the reaction can be first- or second-order, with respect to T^{++} , according to concentration [76JCS(P2)1567].

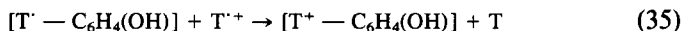
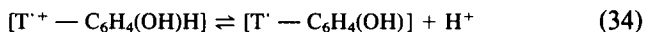
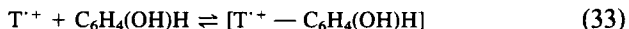
Generating T^{++} electrochemically, then examining its *S*-arylation with anisole, 2,6-dimethylanisole, cumene, and 1,4-dimethoxybenzene, showed that the exact mechanism depends on the oxidation potential of the particular aromatic component: When high, relative to thianthrene, a sequence summarized by Eqs. (28)–(30)

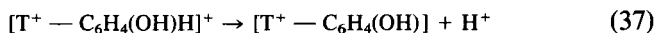
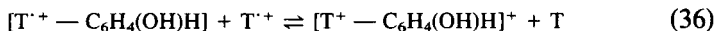


is followed, and when the potentials are similar, Eqs. (31), (32), and (30) describe the process (75JA101; 79BSF282).



In CH_2Cl_2 or CH_2Cl_2/TFA , *S*-arylation with phenol was shown to have both first- and second-order segments; Eqs. (33)–(37) illustrate this. Thus, in neutral solution, the process in Eq. (34) is fast and precludes the process shown in Eq. (36); in acidic solution the step shown in Eq. (34) is inhibited (76JA997).





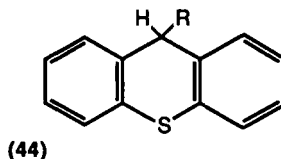
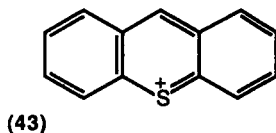
Combining thianthrene radical ion(1+) with free radicals to produce thianthrenium salts has also been achieved. Decomposition of various cumene hydroperoxides (83MI6) and of azobis(2-phenoxy-2-propane) (85MI1) gave 5-arylthianthrenium ions together with 5-(propen-2-yl)thianthrenium perchlorate in the latter case.

S-Alkylation of thianthrene radical ion(1+) with Grignard reagents is not efficient because single electron transfer (SET) processes intervene, leading to the production of complex mixtures containing products derived from alkyl radicals (85PS111; 86T6111). Dialkyl- and diarylmercury reagents do, however, react efficiently with T^+ , producing 5-R-thianthrenium perchlorates (R = Me, Et, 4-Me-C₆H₅, 2-Me-C₆H₅, 4-Cl-C₆H₅, 3-Cl-C₆H₅, and 4-MeO-C₆H₅), and as byproducts, thianthrene in somewhat larger than molar quantity, and R(Ar)HgClO₄ (78JPC1168). Electron-transfer processes may be involved in these S-addition reactions (85PS111), but side products derived from electron-transfer-generated alkyl radicals were a complication only in the case of diethylmercury (83JOC143).

vi. *Reduction of thianthrene radical ion(1+).* Thianthrene radical ion(1+) perchlorate is cleanly reduced to thianthrene using either potassium iodide (69JOC3368) or triphenylphosphine [85IJC(B)995].

vii. *Thianthrene radical ion(1+) as a radical reagent.* A degassed solution of thianthrene radical ion(1+) perchlorate in acrylonitrile is stable for months. However, styrene, methylstyrene, and methyl vinyl ether, but not 1,1-diphenylethene, were polymerized in contact with the radical ion (69JOC3368), and the ion has been recommended for polymerization of THF (see also 85PS111) and oxetane (82MIP1).

Thianthrene radical ion(1+) perchlorate was employed to effect one-electron oxidation of Cu(TPP) (TPP, tetraphenylporphyrinate) to [Cu(TPP')]⁺[SbCl₆]⁻ (82JA6791). It was also used to dehydrogenate thioxanthene (44)(R = H), forming perchlorate 43 or, in the presence of an electron-rich aromatic, the 9-Ar-substituted-thioxanthene 44 (R = Ar) (80MI4; 82MI4) or, in the presence of a phosphine, phosphonium salts 44 (R = P⁺R'₃) (81MI7).



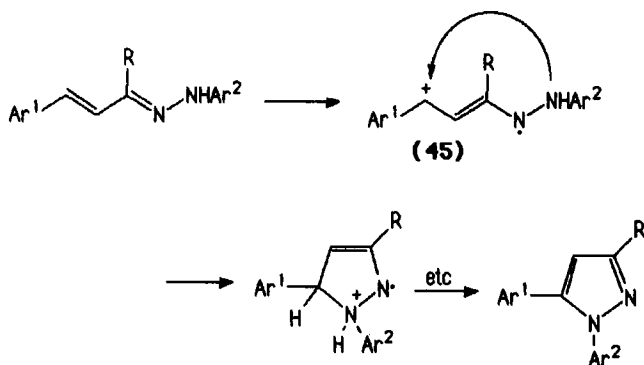
1,1-Azoadamantane exposed to 2 mol equivalents of $T^{\cdot+}$ ClO_4^- at room temperature rapidly and quantitatively evolved nitrogen, and thianthrene and products derived from the adamantyl cation were obtained. Equations (38)–(40) (AA, azo-adamantane; Ad, adamantane) make clear why 2 mol equivalents of the radical oxidant are required (85JA2561). The comparable interaction of $T^{\cdot+}$ with phenylazotriphenylmethane and di-*tert*-butyl diazene, using a 2:1 ratio of radical cation to substrate, also leads to the formation of thianthrene and nitrogen (85PS111).



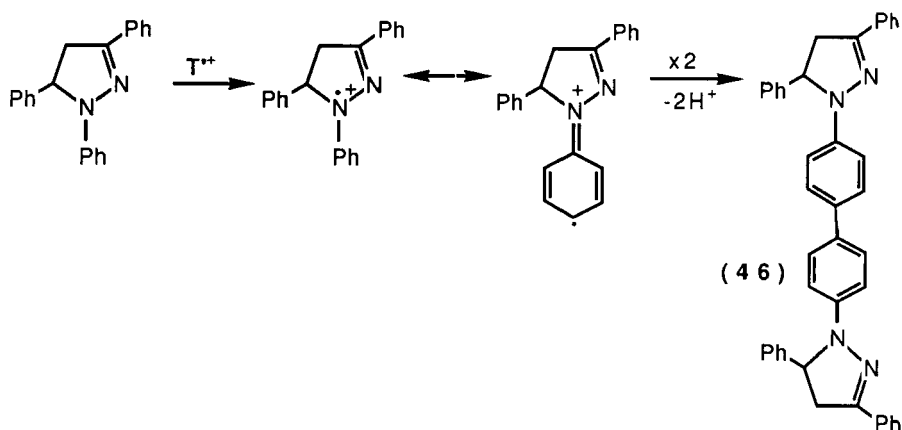
Arylhydrazones of β -aryl- α,β -unsaturated ketones are converted into pyrazoles by 3 mol equivalents of $T^{\cdot+}$ ClO_4^- (Scheme 2). The ring closure occurs via radical cation **45** and is not simply oxidation of a preclosed dihydropyrazole, as evidenced by dimerization (\rightarrow **46**) of such a possible intermediate upon treatment with the radical cation (Scheme 3) (88JOC1973).

The radical cations (**47**) produced by $T^{\cdot+}$ oxidation of aryl aldehyde hydrazones acted as 1,3-dipoles in reaction with nitriles to form, after a second $T^{\cdot+}$ oxidation, 1,2,4-triazoles (Scheme 4) (85TL5655).

An intriguing use of the oxidative potential stored in thianthrene radical ion(1+) is provided by the formation of high-energy phosphate bonds. Thus, the interaction of adenosine-5'-phosphate (AMP) and orthophosphoric acid, each as their ammonium salts, with two equivalents of thi-

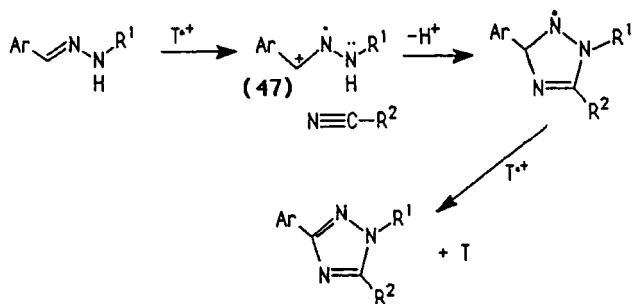
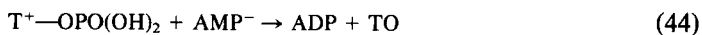
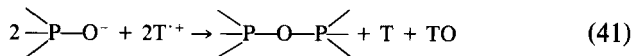


SCHEME 2



SCHEME 3

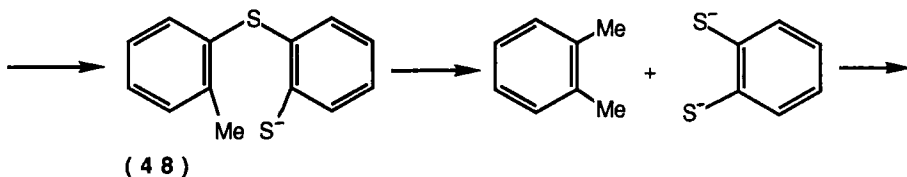
anthrene radical ion(1+) perchlorate in acetonitrile led to adenosine-5'-diphosphate (ADP), and adenosine-5'-triphosphate (ATP), with thianthrene and its 5-oxide as byproducts. 2,3,7,8-Tetramethoxythianthrene radical ion(1+) was somewhat more efficient. The stoichiometry shown in Eq. (41) led to the proposal of a kinetic scheme summarized in Eqs. (42)–(44) (74B2800).



SCHEME 4

4. Nucleophilic Attack

There are no examples of nucleophilic substitution of hydrogen on thianthrene. Methylmagnesium iodide, in the presence of [1,3-bis(diphenylphosphino)propyl]nickel dichloride caused ring opening, probably initially via **48**; *o*-xylene, from a second organometallic attack, and, by

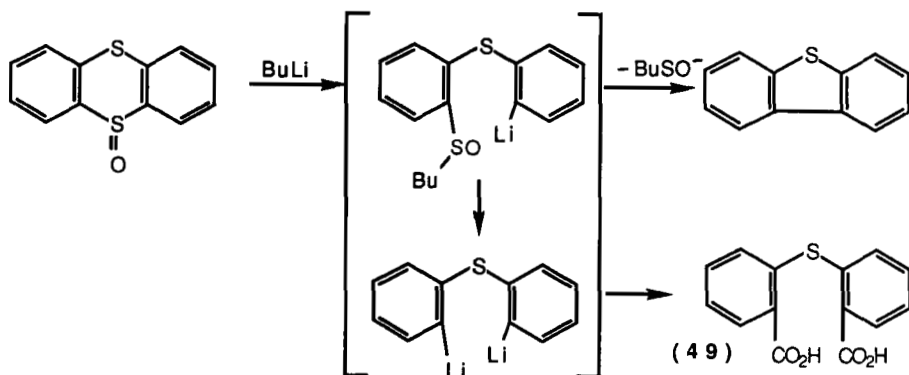


dint of trapping with added iodomethane, 1,2-bismethylthiobenzene were the isolated products (85JOC3828). Fusing thianthrene-2-sulfonic acid 5,5,10,10-tetroxide with sodium hydroxide gave 2-hydroxythianthrene 5,5,10,10-tetroxide (75URP71378).

The ring lithiation of thianthrene had already been thoroughly studied by 1960 (66HC1155); it proceeds specifically at C-1, ortho to sulfur, and provides the means for 1-carboxylation and 1-amination (43JA1461; 57JA108; 64JOC21) and, after exchange to the magnesio derivative, 1-hydroxylation (54JA5787; 57JA991). 2-Bromothianthrene can be converted into its lithio derivative and hence into 2-aminothianthrene (55JA5944; 64JOC21) and thianthrene-2-carboxylic acid (63MI1). Thianthrene 5,5-dioxide is lithiated at C-4, i.e., ortho to the sulfone rather than the sulfide, at -70° . Thianthrene itself is not lithiated under these conditions (55JA3387; 56JOC1278; 57JA108). At room temperature, the use of phenyllithium allows dilithiation of thianthrene 5,5-dioxide and hence, by quenching with carbon dioxide, the preparation of thianthrene-4,6-dicarboxylic acid 5,5-dioxide.

Attempted metallation of thianthrene 5-oxide led, even at -70°C , to ring cleavage and, upon quenching, to a complex mixture of products, with dibenzothiophen as the main product. Attack by the metallating agent at sulfoxide sulfur is viewed as the initiating step (55JA3387; 56JOC1278). A comparable cleavage occurs upon treatment of the sulfoxide with Grignard reagents, though in this case, the intramolecular attack does not take place. Instead, a second intermolecular displacement of sulfur occurs, and after carboxylation, **49** was isolated; small amounts of this were also obtained in the butyllithium sequence (Scheme 5).

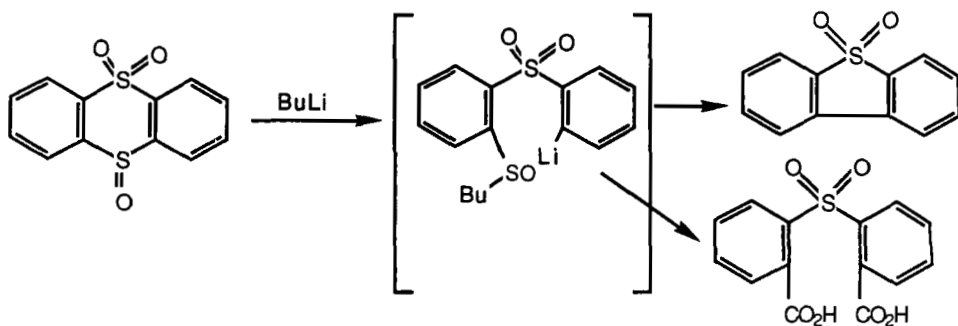
When thianthrene 5,5,10-trioxide is exposed to butyllithium, via attack at the sulfoxide sulfur, dibenzothiophen sulfone and the diphenylsulfide diacid sulfone were the observed products, the latter predominating (Scheme 6) (57JA108).

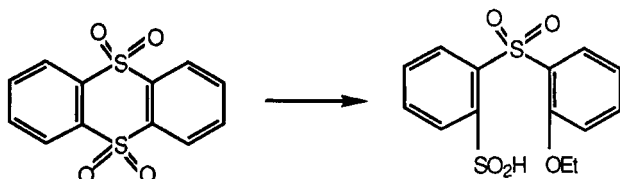


Thianthrene 5,5,10,10-tetroxide can be ring cleaved, even with potassium hydroxide, in hot ethanol (Scheme 7) (11LA312).

There is considerable interest in the reductive removal of sulfur from thianthrene in the context of the presence of thianthrene and other sulfur-containing compounds in coal and the production of "cleaner" fuels. No sulfur was removed when thianthrene was subjected to hydrogen at 100 kp over MoS_2 , until the temperature reached 240°C ; 98% was removed at 340°C , giving mainly benzene and some cyclohexane (66CCC2202). Studies with $\text{NiO}/\text{MoO}_3/\gamma\text{-Al}_2\text{O}_3$, presulfided with $\text{H}_2\text{S}/\text{H}_2/350^\circ\text{C}$ and used at $250^\circ\text{C}/\text{H}_2/40$ bar, showed benzene to be the major product, formed via diphenyl disulfide; this first step was twenty times faster than hydrogenolysis of dibenzothiophen (81BSB1285; 86MI2).

Desulfurization was $\geq 80\%$ effective over $\text{MoO}_3/\text{CoO}/\text{SiO}_2/\text{Al}_2\text{O}_3$ at $350^\circ\text{C}/\text{H}_2/85$ bar (78MI3). The use of $\text{MoS}_3/250\text{--}400^\circ\text{C}/25\text{--}75$ kg cm^2 was





SCHEME 7

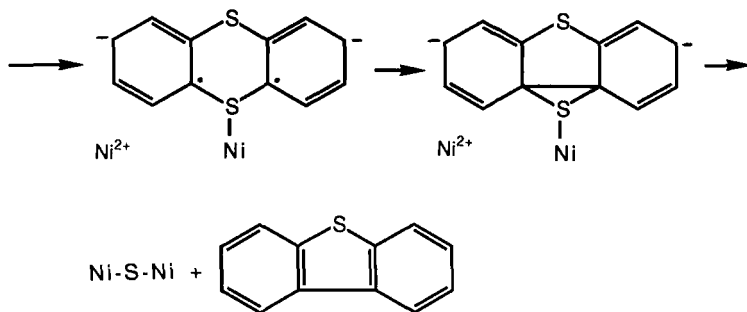
said to be 100% effective in C—S—C hydrogenolysis (73YGK154), and the use of commercial Co/Mo/ γ -Al₂O₃ catalyst was effective even on 1,4,6,9-tetramethylthianthrene, a thianthrene hindered around the sulfur atoms, giving *p*-xylene cleanly (78MI2; 81MI3). The folded shape of thianthrene is believed to allow more appropriate (84BSB653) adsorption than comparable, planar, aromatic, sulfur-containing heterocycles, such as dibenzothiophen (78BCJ1422, 78MI2), which is hydrogenolyzed 10 times slower (84BSB653). Presulfided Ni/W/SiO₂/Al₂O₃ was compared with a presulfided Co/Mo/Al₂O₃ catalyst; at 350°C hydrogenolysis to benzene, diphenyl sulfide, and diphenyl disulfide took place (78BCJ1422).

Organometallic chemical reducing agents have been examined in this context: two molar equivalents of (2,2'-bipyridyl)(1,5-cyclooctadiene) nickel (0) [(bpy)(COD)Ni(0)] converted thianthrene, over 48 hrs at 55°C, into dibenzothiophen (55%) and diphenyl sulfide (15%), while the addition of LiAlH₄ to the catalyst generated a species, LiAlH₄(THF)_n(bpy)Ni(0), which under the same conditions gave diphenyl (15%), dibenzothiophen (5%), traces of benzene, and starting thianthrene, but mainly diphenyl sulfide (75%) (86JA7763).

A complex reducing agent (CRA), dubbed NiCRA-bpy, was 99% effective in converting thianthrene into diphenyl over 18 hrs; over 89 hrs, benzene (83%), diphenyl (8%), and dibenzothiophen (3%) were the products. The reductant was a 4 : 2 : 1 : 2 mixture of NaH, *t*-AmONa, Ni(OAc)₂, and bpy (88TL2963).

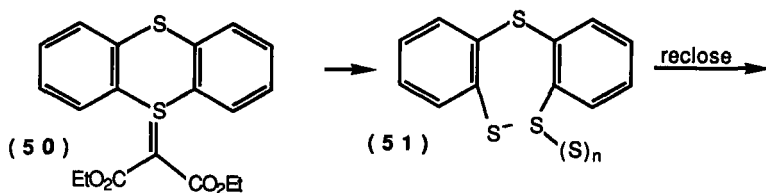
Thianthrene was inert to (COD)₂Ni(0) alone, but treatment with 2 mol equivalents of the nickel species in the presence of 2 mol equivalents of bpy converted it into dibenzothiophen (60%) and diphenyl (10%). The active desulfurizing agent was considered to be (bpy)(COD)Ni(0), the requirement for two metal equivalents being that one coordinates a sulfur the other effects rupture of the ring; Scheme 8 illustrates this (77JOM51).

Exposure of thianthrene to Na/NH₃(liq) caused cleavage of the ring; phenylthiol and diphenyl disulfide were the observed products (61YZ13).



5. Carbenoid and Radical Attack

There is just one example of the reaction of thianthrene with a carbene, generated either by decomposition of diethyl diazomalonate at 140°C in the presence of CuSO_4 (82JHC833) or using $\text{PhI}^+-\text{C}^-(\text{CN})_2$ as a precursor [87JCR(S)374] and producing **50**.

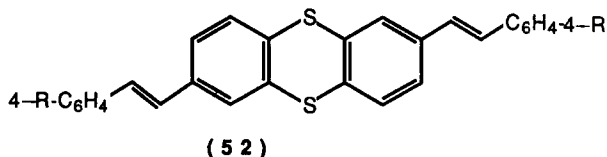


The substitution of thianthrene with radicals does not appear to have been examined. Reaction with ^{35}S at 320°C produced thianthrene in which 83% of the sulfur had been exchanged; an intermediate of the form **51** was suggested (73BCJ650).

B. REACTIVITY OF SUBSTITUENTS

1. General Survey

Generally, C-substituents on thianthrenes behave as normal aryl sulfide substituents, and few abnormalities have been noted (see later). The reaction of thianthrene sulfoxides and sulfones, too, are representative of those classes of functional groups.



2. Substituents at Carbon

a. *Alkyl, Acyl, and Carboxyl.* There are two examples of the condensation of the, apparently unactivated, methyl groups of 2,7-dimethylthianthrene with imines. Treatment with two arylaldehyde aniline Schiff bases, in the presence of solid KOH, gave the styryl derivatives **52** ($R = H$ and *i*-Pr) (69HCA1282).

Attempted simple oxidation of alkyl groups on thianthrenes would also effect *S*-oxidation. However, sulfones *can* be side-chain-oxidized: 2,3,6,7-tetramethyl-, 1,2,7,8-tetramethyl-, 1,4,6,9-tetramethyl-, and 1,3,7,9-tetramethylthianthrene tetroxides gave the tetra-acids with 25% HNO_3 at $220^\circ C$. These tetra-acids were converted to esters and anhydrides in the usual ways (69USP3410868).

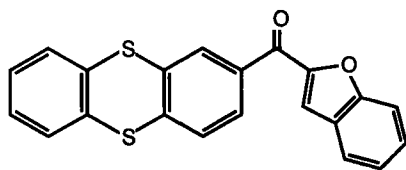
2-Mono- and 2,7-diacetylthianthrenes have been converted into the acid(s) by hypohalite (61RC745; 62MI2; 63MI1; 66RC1021), chromic acid (\rightarrow thianthren-2-carboxylic acid tetroxide) (62MI1), and alkaline permanganate (\rightarrow thianthrene-2,7-dicarboxylic acid tetroxide) (64MI1; 87MI3) oxidations. Conversion of 2-mono- or 2,7-diacetylthianthrenes to oxime/dioxime and hence to amine/diamine via Beckmann rearrangements is the standard method for the formation of these bases (62MI1; 73BSF1460; 79MI3). The Wilgerodt reaction has been used to produce thianthren-2-ylacetic acid, which was derivatized (61RC745; 62MI1; 66RC1021), and 2,7-diacetylthianthrene to give thianthrene-2,7-diacetic acid (62MI3). The Arndt-Eistert procedure (61RC745; 62MI2) also gave the 2-acetic acid. (See Section III, A, 3, a [80JCS(P1)1185] for complications that prevented the use of this procedure for the 1-isomer.)

Thianthrene-1-carboxylic acid can be decarboxylated upon heating (43JA1461). Both diazomethane (62MI2) and alcohol- H^+ (61RC745; 62MI1; 64MI1; 66RC1021; 87MI3) methods have been employed for esterification of thianthrene and thianthrene-oxide acids. Acid chlorides, amides, and hydrazides of thianthrene acids form normally (61RC745; 62MI3; 64MI1; 87MI3). The use of diamines with the bis acid chloride of thianthrene-2,7-dicarboxylic acid tetroxide produced polyamide polymers (87MI3). Heat-stable and fiber-forming polyimides were produced by condensing thianthrene-2,3,7,8-tetracarboxylic acid bisanhydride tetroxide

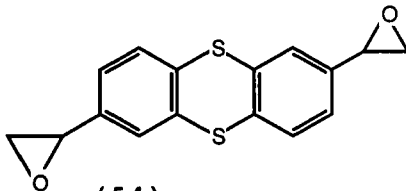
with diamines (70USP3502625). The polymeric ketone produced by acylating thianthrene, presumably at 2- and 7-positions, with adipoyl and isophthaloyl chlorides was subjected to the Schmidt reaction with $\text{NaN}_3/\text{H}_2\text{SO}_4$, giving rise to the corresponding polyamides (82MI7). Polyamides were formed from diamines and thianthrene-2,7-bis(4-oxobutanoic acid) (88MI5).

2-Acetyl- (62MI1; 73BSF1460) and 2,7-diacetylthianthrene have been used as ketone components in Friedlander quinoline-4-carboxylic acid syntheses. In the latter case, they were used to generate polymers by using diamino-ketones as the other component (87MI6). 2-Acetylthianthrene undergoes normal base-catalyzed aldol condensation (62MI1).

Meerwein-Ponndorff-Verley reduction of 2-acetylthianthrene gave the alcohol, the acetate of which afforded 2-vinylthianthrene when heated at 500°C ; the vinylthianthrene was copolymerized with acrylates (63MI1). Sodium borohydride also reduces the ketone to the alcohol (70JMC620). Wolff-Kishner reductions of 2-acetyl-, 2-benzoyl-, and 2,7-diacetylthianthrenes gave the corresponding alkyl-substituted thianthrenes (73BSF1460). Reduction of ketone **53**, formed by condensing 2-bromoacetylthianthrene with salicaldehyde, also proceeded straightforwardly (73BSF1460). However, subjecting 2,7-bischloroacetylthianthrene to the conditions of the Meerwein-Ponndorff-Verley reduction, then to base, gave the bis-epoxide **54** (62HCA982).

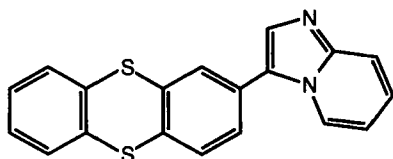


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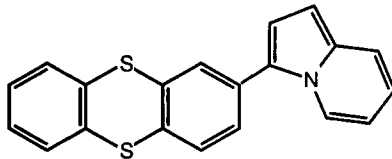


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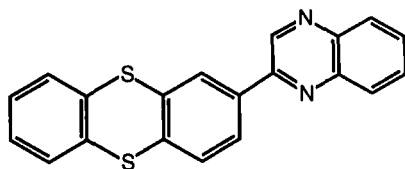
2-Bromoacetylthianthrene, which can be produced by direct acylation as well as via bromination of 2-acetylthianthrene (63MI2) (for comparable dibromination of 2,7-diacetylthianthrene, see 64MI1), has been used in its capacity as an α -bromo-ketone to produce thianthren-2-yl-substituted heterocycles such as **55**, **56**, **57** (63MI2; 73BSF1460), and 2-amino-4-(thianthren-2-yl)thiazole (63MI2), by condensation with 2-aminopyridine,



(55)



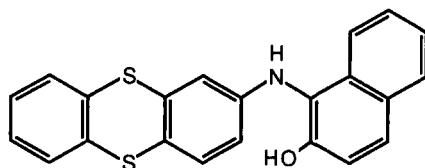
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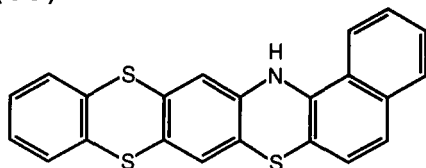
(5 7)

2-picoline, *o*-phenylenediamine, and thiourea, respectively. 2-Bromoacetylthianthrene was degraded to the 2-acid by treatment with pyridine and then NaOH (64MI1).

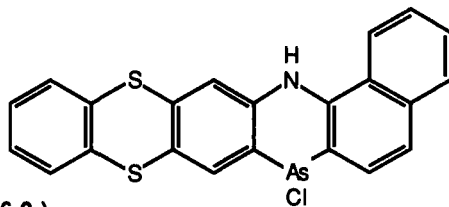
b. *Nitrogen*. 2-Aminothianthrene reacted with β -naphthol to give **58**, which was then used in the synthesis of more complex polycyclic heterocycles. For example, upon reaction with sulfur at 200°C, **59** was obtained; and with AsCl₃, the heterocycle **60** was produced (73BSF1460).



(5 8)



(5 9)



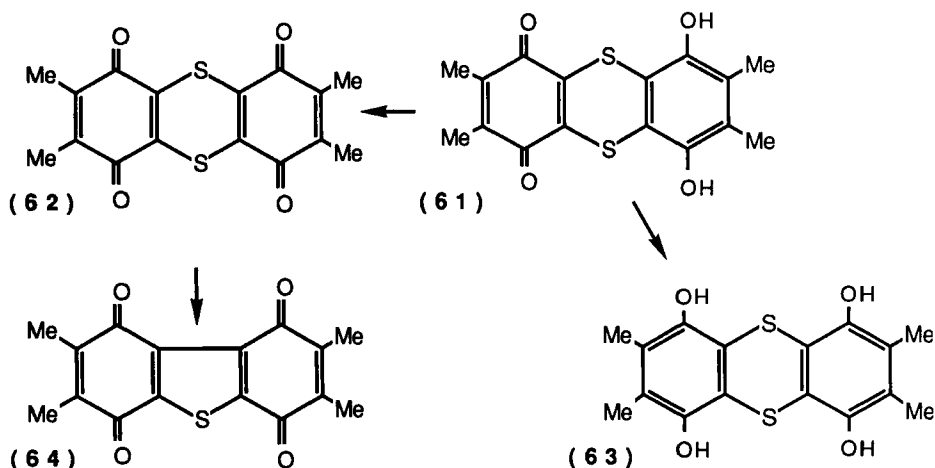
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2,7-Dinitrothianthrene is reduced to the diamine with Zn-HCl (84ZOR202) or Fe-AcOH (83SC1181); Zn-AcOH gave the diacetamide (83SC1181). 1- and 2-Aminothianthrenes can be diazotized and the resulting salts subjected to standard Sandmeyer and coupling processes (23JCS156; 37JCS1592; 57JA108). The 2,7-diamine could be diazotized

and hence converted into 2,7-dichlorothianthrene (83SC1181). Usefully, ammonium polysulfide rapidly effected partial reduction, giving 2-amino-7-nitrothianthrene, the diazonium salt from which could be reduced (\rightarrow 2-nitrothianthrene), or which can be converted into 2-chloro-7-nitro- or 2-thiocyano-7-nitrothianthrenes (83SC1181).

A number of investigations of polyamides, produced from 2,7- and 2,8-diaminothianthrenes by reaction with diacid chlorides or dianhydrides [\rightarrow polyimides (79MI3; 81MI2; 88MI4)], have been described [76JAP(K)5196893; 80MI2; 81MI5, 81MI10; 86MI5].

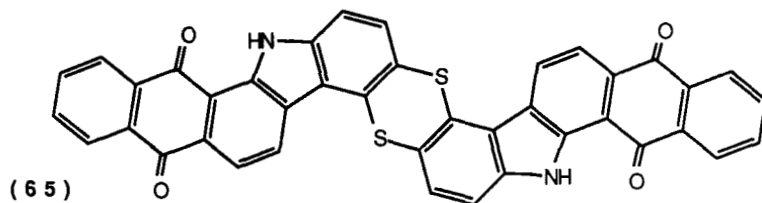
c. Oxygen. Oxidation of the blue-violet quinone-diphenol **61** with *c.* HNO_3 gave the red-violet bisquinone **62**, and conversely, reduction with $\text{Na}_2\text{S}_2\text{O}_4$ gave the tetraphenol **63**. The bisquinone was converted cleanly to mono-*S*-oxide with peracetic acid at room temperature, but heating during this reaction, or heating the sulfoxide, led to extrusion of SO and the formation of dibenzothiophen bisquinone **64** (69CB1739).



The thianthrene ring system survives standard phenolic *O*-demethylation procedures, thus, 2,7-dimethoxythianthrene (HBr) (15 LA194) and 2,3,7,8-tetramethoxythianthrene (HI) (29LA162) were converted to the bis- and tetrakis-phenols. It was shown that the 2,7-dihydroxythianthrene is brominated at each of the positions ortho to the hydroxyl groups (15LA194).

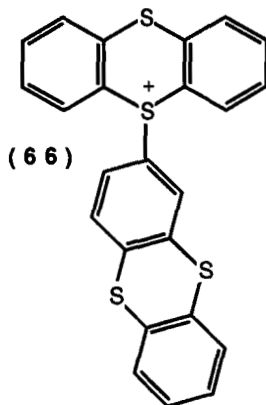
d. Halogen. The lithiation and, hence, carboxylation (57JA108) of 2-bromothianthrene was used to confirm the regioselectivity of bromination and acetylation (63MI1). The 2-lithio-derivative gave 2-amino-

thianthrene upon reaction with methoxyamine (55JA5944). Hydrolysis of 2-bromothianthrene to the phenol was possible with NaOH at 250°C (35GEP427816). Octafluorothianthrene reacted slowly but efficiently with hot MeONa-MeOH to give 2-methoxyheptafluorothianthrene (68T2783, 68T3997). A patent states that 2,7-dibromothianthrene, upon treatment first with 1-aminoanthracene-9,10-dione in the presence of Na₂CO₃-Cu and then with AlCl₃/NaCl/180°C, cyclizes to produce a material of probable structure **65** (64USP3106563).

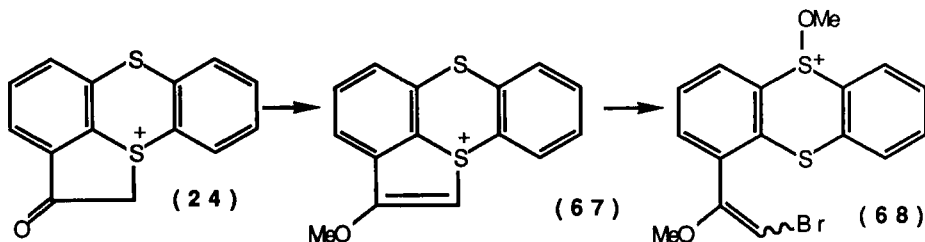


3. Substituents at Sulfur

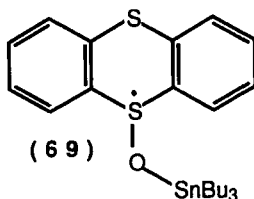
a. *Alkyl, Alkenyl, and Aryl.* 5-(Thianthren-2-yl)thianthrenium perchlorate **66** was cleaved by sodium naphthalenide at -78°C in the presence of phenyl thiol, giving as main products thianthrene (66%) and 2-phenylthiothianthrene (33%) (87MI1). 5-(4-Cyanobenzyl)thianthrenium



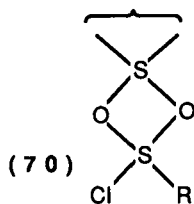
perchlorate alkylated acetonitrile, giving, after hydrolytic work-up, thianthrene and the 4-cyanophenylmethylamide of acetic acid. The same salt polymerized THF (86T6123). The tetracyclic keto-thianthrenium **24** was converted to the enol ether **67** using CH₂N₂, and this underwent a remarkable reaction with Br₂ in MeOH, producing a compound assigned structure **68** [80JCS(P1)1185].



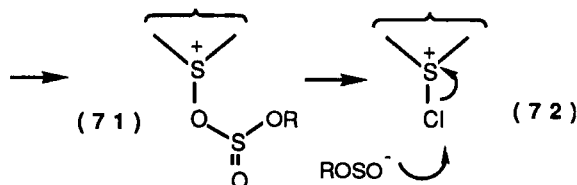
b. *Oxygen*. The clean reduction (see also 88T6537) of thianthrene oxides to thianthrene can be achieved in a number of ways. Classically, Zn/AcOH will reduce both thianthrene 5-oxide and the 5,10-dioxide to the parent heterocycle (1896CB435), but will reduce the 5,5,10-trioxide to thianthrene 5,5-dioxide (55JA5944). The monoxide is transformed in very high yield to thianthrene with HBr at room temperature (11LA312; 55JA5944). Bu_3SnH /AIBN reduction was rationalized as proceeding via



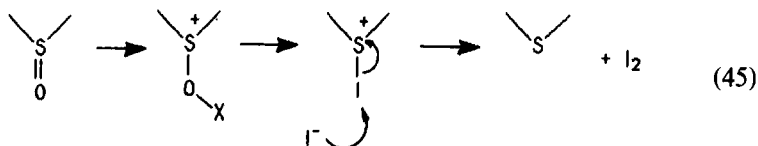
69 [74CI(L)496]. It would be interesting to establish whether radical intermediates are also involved when thianthrene 5-oxide is reduced (65%) with *N*-benzyl-1,4-dihydronicotinamide in the presence of 5% *meso*-tetraphenylporphyrinate iron(III) chloride (84TL341). The high yield obtained using aryl- or methylsulfinyl chlorides (the byproducts being the sulfonyl chloride) are explained by an intermediate **70** ($\text{R} = \text{Ar}$ or Me) or



the sequence $\rightarrow \mathbf{71} \rightarrow \mathbf{72} \rightarrow$ (76OPP119). This process may be related mechanistically to the reduction brought about by acetyl chloride; chlorine and acetic anhydride are the byproducts in this case [73CI(L)277]. More conventionally, iodide in the presence of HClO_4 (71BCJ2456) or $\text{BF}_3 \cdot \text{Et}_2\text{O}$



(83PS19), the latter at 0°C, are very efficient. A sequence generalized in Eq. (45) ($X = \text{H}$ or BF_3) is believed to operate. A quantitative deoxygenation was achieved with $\text{Zn}/1,4\text{-dibromobutane}$ at 150°C (87CPB4351).



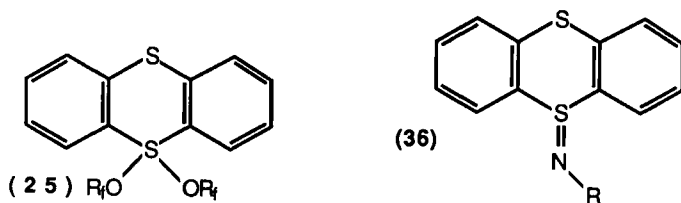
Sulfur, at 345°C for thianthrene tetroxide, or at 250°C for thianthrene 5-oxide, produced thianthrene in good yields. ^{35}S -Labeling experiments showed that the former took place with 80% replacement of ring sulfur and the latter took place with 91% replacement (73BCJ650), so these processes, whatever their detailed mechanism, do not involve simple reductive cleavage of the S—O bond. In accordance with this, thianthrene 5,5,10,10-tetroxide is converted into selenanthrene by reaction with elementary selenium (1896CB443).

Treated with *c.* HCl (65JOC2145) or *c.* H_2SO_4 , then ice (63JOC2828), thianthrene 5-oxide gave 2-substituted-products: 2-chloro (in low yield) and 2-hydroxythianthrene 5-oxide, the latter being reduced to 2-hydroxythianthrene by subsequent exposure to Sn/AcOH . Thianthrene radical ion(1+) may be produced in each case; thus the incorporation of phenol into the HCl reaction gave the 5-(4-chlorophenyl)thianthrenium chloride (65JOC2145) (see Section III, A, 3, b).

cis- and *trans*-isomers of thianthrene-2-carboxylic acid 5,10-dioxide were prepared; the *cis*-isomer isomerized to *trans* above 260–290°C (62MI2). Initial claims to have oxidized optically-active *cis*- and *trans*-thianthrene-2-carboxylic acid 5,10-dioxides to optically-active tetroxides (66RC1243) were later discounted (67JA4815) when it was shown that optically *inactive* thianthrene-2-carboxylic acid tetroxide is obtained by mild oxidation of *either* (–)-*cis* or (+)-*trans* isomers, illustrating the conformational mobility of the thianthrene tetroxide nucleus. *cis*- and *trans*-thianthrene 2-acetic acid 5,10-dioxides have been resolved (71RC1879).

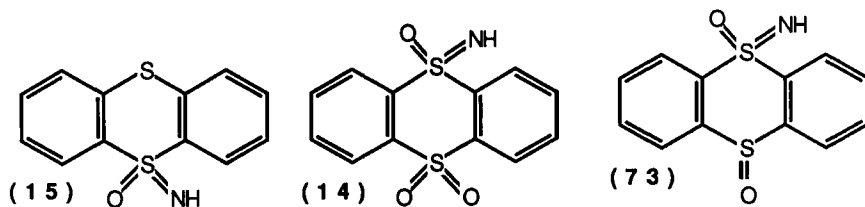
c. Halogen and Nitrogen. 5,5-Dihydro-5,5-dibromothianthrene transfers the halogen to the selenium of phenoxaselenine (70RRC1967).

The sulfurane **25** reacts with benzylamine, producing thianthrene 5-oxide and the sulfoximine **36** ($R = \text{CH}_2\text{Ph}$). The latter was hydrolyzed by sequential

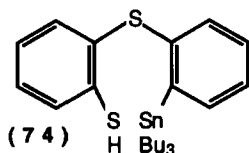


treatments with acid, then alkali, to afford thianthrene 5-oxide (77JOC3222).

It was claimed that thianthrene sulfoximine **15** is formed by reaction of thianthrene 5-oxide with arylsulfonyl azide, followed by hydrolysis; it was possible to alkylate **15** on nitrogen (76GEP2417063). Using hydrazoic acid, sulfoximine-sulfoxide **73** was produced from *cis*- or *trans*-thianthrene 5,10-dioxide, but no reaction occurred with thianthrene 5-oxide or the 5,5,10-trioxide. Permanganate oxidation of **73** gave the sulfoximine-sulfone **14** whereas, peracetic acid afforded thianthrene-5,5,10,10-tetroxide (74JHC839). Periodate oxidation of 5,5-dihydro-5-iminothianthrene took place at the sulfoximine sulfur, giving **15** (74TL1973). Treatment of 5,5-



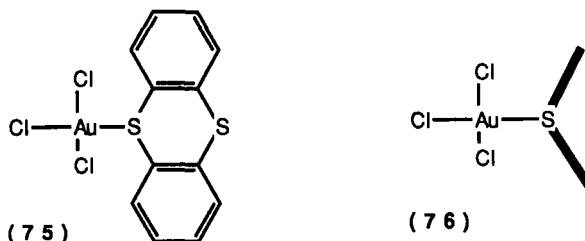
dihydro-*N*-tosyliminothianthrene with $\text{Bu}_3\text{SnH/AIBN}$ gave thianthrene (30%), an equal amount of ring-cleaved stannane **74**, and tosylamide, quantitatively [74CI(L)496].



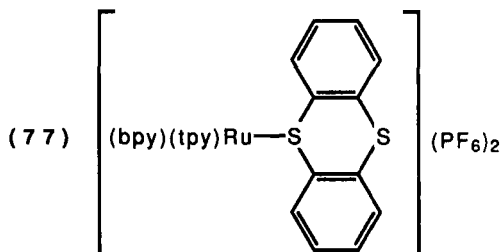
C. ORGANOMETALLIC COMPLEXES

Thianthrene complexes in solution with Ag(I) via a sulfur (70OMR491). It seems that thianthrene can serve as a mono- or a bidentate ligand. Thus,

reaction with chloroauric acid gave a dark red crystalline material **75**, in which the gold atom is 4-coordinated, square planar. The diagram **76** shows the orientation of folded thianthrene to the metal center. The second sulfur (eclipsed in **76**) is not involved at all in bonding to the metal; the metal—sulfur bond is oriented axially with respect to the thianthrene central boat [78AX(B)3364; 80MI3]. Complexes TRhCl₃ and T₃IrCl₃ have also been described (80MI3).

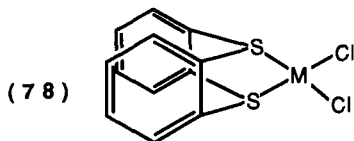


A comparable monodentate role, but without crystallographic support, was proposed on the basis of UV spectroscopic analysis for complex **77** from reaction of [(bpy)(tpy)(RuCl)PF₆] (tpy = 2,2':6,2''-terpyridine) with thianthrene and Ag⁺ at room temperature (85IC1464).



No role other than “seems to be acting as a chelate” was attributed to thianthrene in the product, [IrH₂(T)(PPh₃)₂]BF₄, when *cis*, *cis*, *trans* [IrH₂(Me₂CO)₂(PPh₃)₂]BF₄ was treated with thianthrene. Because the two aromatic rings in the heterocycle are equivalent (¹H-NMR) in the complex, it was deduced not to be a η⁶-arene complex (which would in any case have violated the 18-electron rule). The thianthrene was not strongly bonded, being displaced by treatment with acetonitrile. That two acetone molecules are displaced in its formation, and that it is in turn displaced by two acetonitrile molecules, seems to suggest a bidentate role for the heterocycle in this complex (83MI2).

Bidentate roles are ascribed to the thianthrene in the yellow dichlorobis(thianthrene)palladium(II) and dichlorobis(thianthrene)platinum(II) solids formed in high yields by reaction of thianthrene in ethanol with



PdCl_2/HCl and H_2PtCl_6 , respectively. However, structures such as **78**, in which the metal coordination is approximately square planar, can be considered no more than probable in the absence of crystallographic support. UV-VIS spectroscopic evidence was offered for nonisolable 1:2 complexes [76JCS(D)1072].

In an X-ray crystallographic study that clearly demonstrated bidentate coordination between 2,3,7,8-tetramethoxyselenanthrene and a platinum center, and between 2,3,7,8-bismethylenedioxyselelanthrene and a mercury center, complexes of analogous thianthrenes were obtained for which a similar mode of liganding is therefore implied, but was not proved by X-ray crystallography. Thus, the dark yellow $\text{PtCl}_2 \cdot 2,3,7,8-(\text{MeO})_4\text{-T}$ and $\text{PtCl}_2 \cdot 2,3,7,8-(\text{OCH}_2\text{O})_2\text{-T}$, and the colorless $\text{AgNO}_3 \cdot 2,3,7,8-(\text{MeO})_4\text{-T}$ and pale yellow $\text{HgCl}_2 \cdot 2,3,7,8-(\text{MeO})_4\text{-T}$ were isolated as solid materials from reactions between the heterocycles and the metal halides at room temperature. A red 1:2 complex, $\text{PdCl}_2 \cdot (2,3,7,8-(\text{MeO})_4\text{-T})_2$, was also obtained, but no comment was made on its possible structure [86JCR(M)2801, 86JCR(S)326].

Based on analogy with an analogous selenanthrene complex, the crystal structure of which was determined, 2,3,7,8-tetramethoxythianthrene forms complexes $[\text{Re}_2\text{Br}_2(\text{CO})_6\text{T}]$ and $[\text{Pt}_2\text{Cl}_2\text{Me}_6\text{T}]$ upon reaction with $[\text{ReBr}(\text{CO})_3(\text{THF})_2]$ and $[\text{PtXMe}_3\text{Cl}]$ ($\text{X} = \text{Cl}$ and Br). The heterocycle performs a unique bridging role, as illustrated in Fig. 5 (87MI7).

Although thianthrene itself did not form a compound with uranyl halides or nitrate, thianthrene 5-oxide did give yellow solids $\text{UO}_2\text{Cl}_2(\text{TO})_2$,

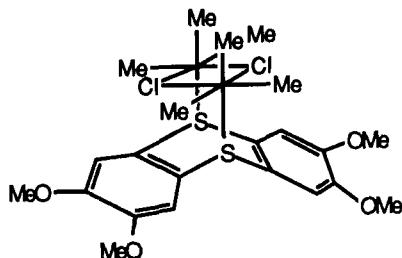
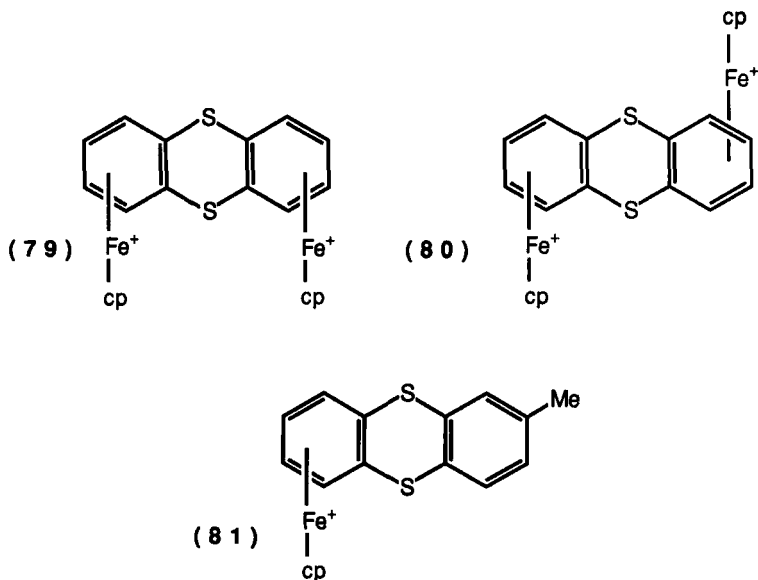


FIG. 5. Bridging role of the heterocycle $[\text{Re}_2\text{Br}_2(\text{CO})_6\text{T}]$ and $[\text{Pt}_2\text{Cl}_2\text{Me}_6\text{T}]$ on reaction with $[\text{ReBr}(\text{CO})_3(\text{THF})_2]$ and $[\text{PtXMe}_3\text{Cl}]$.

$\text{UO}_2\text{Br}_2(\text{TO})_2$, and $\text{UO}_2(\text{NO}_3)_2(\text{TO})_2$ by reaction in ethyl acetate at room temperature. IR evidence was consistent with complexation (presumably monodentate) via sulfoxide oxygen [76IJC(A)135]. Thianthrene 5-oxide also formed a complex $\text{MoCl}_5 \cdot \text{TO}$ by reaction with the metal pentachloride, again by IR analysis, via the oxygen (72MI2). Colorless 1 : 1 adducts, again formed simply by reaction in ethanol, from treatment of cadmium(II) and mercury(II) halides with thianthrene oxides, were $\text{CdCl}_2 \cdot \text{TO}$, $\text{HgCl}_2 \cdot \text{cis-T-5,10-O}_2$, $\text{CdCl}_2 \cdot \text{cis-T-5,10-O}_2$, $\text{HgCl}_2 \cdot \text{trans-T-5,10-O}_2$, and a 2 : 1 adduct, $\text{HgCl}_2(\text{T-5,5,10-O}_3)_2$ [74SA(A)2021]. Diphenyltin dichloride gave a 1 : 1 adduct with thianthrene 5-oxide (82MI1).

The conductivity of crystals of T.Ni(mnt)_2 , grown by electrocrystallization, was $10^{-4} \Omega^{-1} \text{cm}^{-1}$ (80CC356); no comment was made on the structure of the complex.

A 3 : 7 mixture of the *cis*- and *trans*- η^6, η^6 -complexes **79** and **80** resulted from treatment of ferrocene with thianthrene/ Al/AlCl_3 in hot decalin (83JOM357), and a comparable η^6 -complex **81** was obtained directly from a ring synthesis. The surprising orientation of the cyclopentadienyl units in **79**, both in the cleft rather than out of it, was established by X-ray crystallography. There is no interaction between the five-membered ring and the thianthrene (85JOM387). The cyclic voltammetry of η^6 -complex **81** and the *trans* η^6, η^6 -complex **80** have been studied with regard to reduction of the iron centers (87MI4, 88MI2).



D. CHARGE-TRANSFER AND RELATED COMPLEXES

Thianthrene does not form a compound or a solid solution with iodine, (85MI7) though it was shown to be a sulfur lone-pair donor in solution (64JA164). A colorless solid was obtained by crystallizing a solution of thianthrene and tetrachloro nitrobenzene (TCNB), but the material is not a charge-transfer complex. No structure was proposed; the crystals gave a strong, electrical photo-response to light < 340 nm (84MI3). Earlier workers (77CJC766) reported the absence of an ESR signal for the complex, but later, a signal, with g value 2.0025 was detected (87MI8).

2,3,7,8-Tetramethoxythianthrene.TCNQ crystals *are* of the charge-transfer type, having alternate stacking of the two molecules as shown in Fig. 6 (77IZV208, 77ZSK898; 87MI8), and accordingly, having the resistivity of an insulator (77CJC766; 87MI8).

Thermochemical data for the orange charge-transfer complex with pyromellitic anhydride (78G21) and those with tetracyanoethylene (TCNE), trinitrobenzene (TNB), and picric acid (74MI1) have been determined. Solution measurements of fluorescence quenching were used to study the weak complexes with CCl_4 , CHCl_3 , Me_2CO , and dichloroethene [72SA(A)1823]. In the case of acetone, a 1705 cm^{-1} shoulder on the carbonyl stretching band was taken to indicate $n-\pi^*$ interaction.

When 2,3,7,8-tetramethoxythianthrene and 3,4,5,6-tetrachloro-*o*-benzoquinone were heated together in concentrated solution, dark blue crystals of a charge-transfer complex between thianthrene and the dimer of the quinone were obtained. X-ray crystallography showed the interesting stacking in these crystals in which three "roof tiles" align conventionally beside a fourth (a third receptor component), which is at right angles (Fig. 7) [86ZN(B)1133].

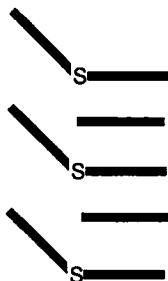


FIG. 6. Alternate stacking of the two molecules of the 2,3,7,8-tetramethoxythianthrene.TCNQ crystal.

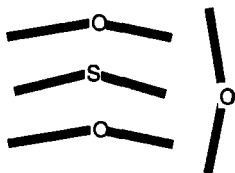
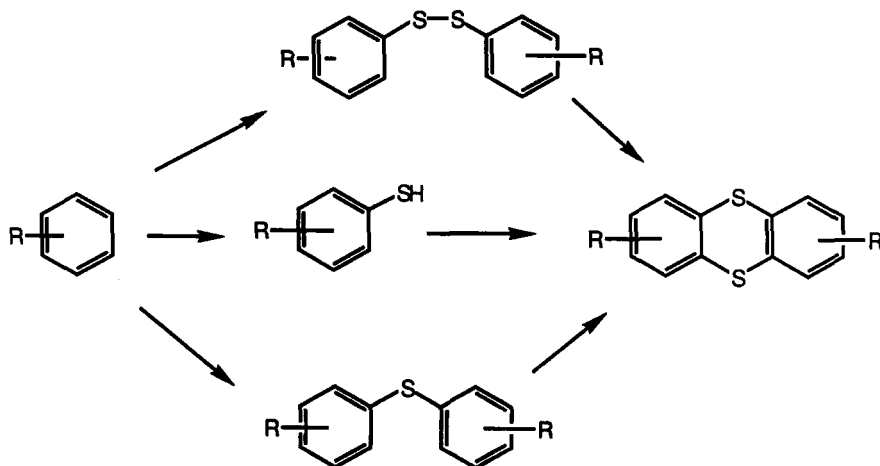


FIG. 7. Stacking of molecules in crystals of a charge-transfer complex between thianthrene and the dimer of quinone.

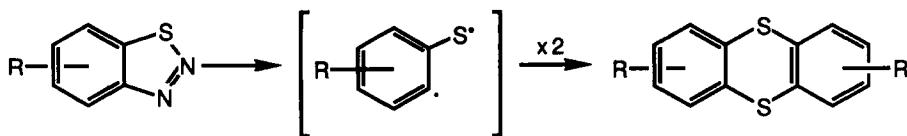
IV. Synthesis of Thianthrenes

A. GENERAL REVIEW AND BACKGROUND

At the time of the earlier review (66HC1155), it was already known that combinations of arenes with sulfur, or with sulfur mono- or dichlorides in the presence of Lewis acids (IV,B,1), or of aryl thiols, diaryl sulfides, or disulfides (IV,B,2 and 3) again heated with Lewis acid catalysts, generate thianthrenes, sometimes in acceptable preparative yields. A complimentary method is the treatment of aryl thiols with *c.* H_2SO_4 . Routes from arenes and aryl thiols almost certainly involve the initial formation of diaryl sulfides. All these methods inevitably give symmetrical thianthrenes carrying identical substituents on each benzene ring (Scheme 9), unless the second sulfur is introduced in a controlled fashion into a preformed, unsymmetrical diphenyl sulfide.



SCHEME 9



SCHEME 10

Thermolysis of 1,2,3-benzothiadiazoles (Scheme 10) (IV,D,1) also suffers from this disadvantage, 2 mol equivalents losing two molecules of nitrogen and dimerizing to give a symmetrically substituted thianthrene.

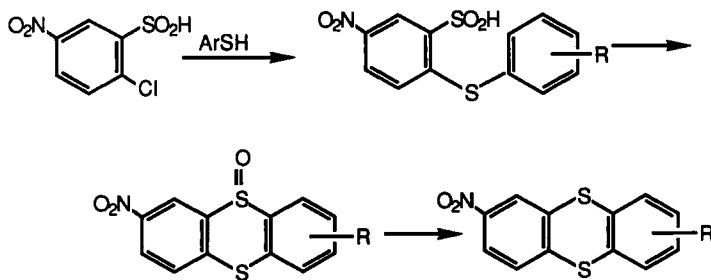
More variation is available when the hetero-ring is closed using the sulfinic acid functionality in a diarylsulfide carrying the sulfinic acid at an ortho position (Scheme 11) (IV,C).

Unsymmetrical thianthrenes can also be obtained by reacting an aryl-1,2-dithiolate with a suitably activated aryl-1,2-dihalide or an equivalent (IV,B,4). All these methods have been further used, the scope of some have been extended, and some have been subjected to mechanistic study.

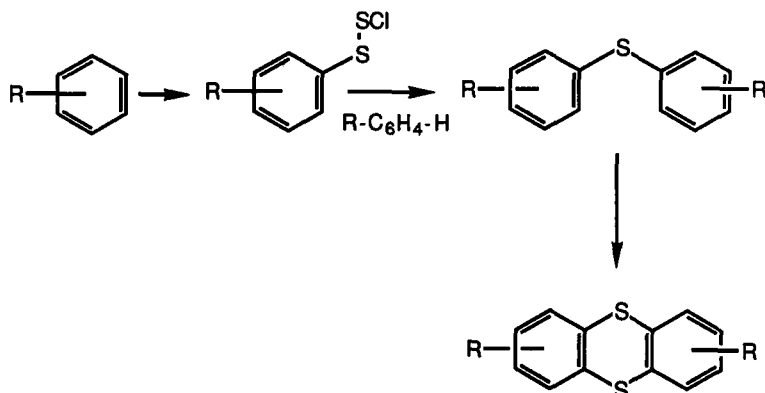
B. SYNTHESSES FROM NONHETEROCYCLIC PRECURSORS

1. From Arenes

Sulfur, benzene, and AlCl_3 heated under various conditions produce a ladder polymer **12** containing thianthrene units, which is probably similar in composition to those obtained by similar treatment of diphenyl sulfide or diphenyl disulfide. It is assumed that diphenyl sulfide is the first formed intermediate (83MI7; 85MI2, 85MI6; 88MI3). 2,3,7,8-, 1,4,6,9-, and 1,3,7,9-tetramethylthianthrenes were obtained in yields of 14–32% from the xylenes, sulfur, and AlCl_3 (71BSF2060).

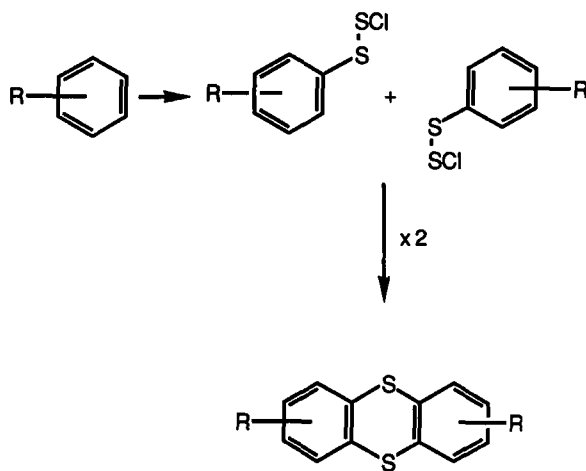


SCHEME 11



SCHEME 12

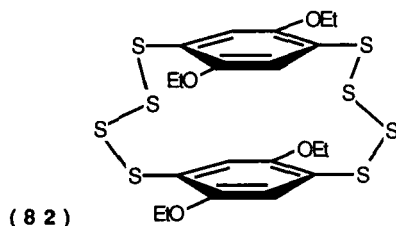
The production of good quality thianthrene using the benzene/ S_2Cl_2 / AlCl_3 route is ensured by work up with ammonia, perhaps to reduce any thianthrene radical ion(1+) present at the end of the reaction (78GEP2739217). In the sulfur monochloride synthesis of substituted thianthrenes, isomeric products would result if the synthesis proceeded as in Scheme 12 or, alternatively, as in Scheme 13 and earlier work (66HC1155) seemed to suggest that either or both of these routes can operate. As another illustration, both 2,7-dimethyl-3,8-dichloro- and 2,8-dimethyl-3,7-dichlorothianthrenes are produced upon reaction of *o*-chlorotoluene with



SCHEME 13

$S_2Cl_2/AlCl_3$ (79GEP2834123). The conversion of preformed $PhSSCl$ into thianthrene upon reaction with benzene/ $AlCl_3$ was cited as evidence that the reaction, at least, *can* proceed via diarylsulfide [72JCS(P1)1687]. Only a trace of octachlorothianthrene resulted from treatment of 1,2,3,4-tetrachlorobenzene with S_2Cl_2 , the corresponding diarylsulfide being isolated in this case (87JOM59). Sulfur dichloride was used as a sulfur source by reacting it with the dilithio derivative from bis(2-bromo-3,4,5,6-tetrafluorophenyl)sulfide (68T2783, 68T3997), giving octafluorothianthrene.

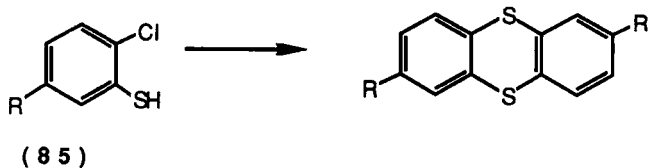
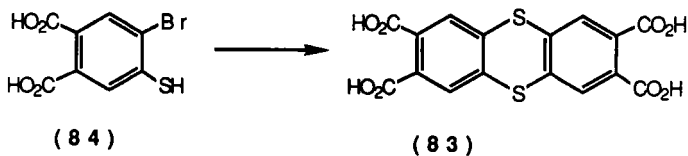
Although a low yield of 2,3,7,8-tetra-alkoxythianthrenes can be obtained from *o*-dialkoxybenzenes/ $S_2Cl_2/AlCl_3$ [72JCS(P1)1687], attempted extrapolation to 1,4-diethoxybenzene produced not the thianthrene, but dimer **82** [69JCS(D)847]. A moderate yield of 2,3,7,8-bismethylenedioxythianthrene resulted from reacting methylenedioxybenzene with SCl_2



[86JCR(M)2801, 86JCR(S)326]. A good yield of 2,3,7,8-tetramethoxythianthrene could be obtained by reacting methylenedioxybenzene with SCl_2 , without Lewis acid catalysis, but with a subsequent reductive treatment using $SnCl_2$ (78LA785). In an analogous synthesis, 1,4-dimethoxy-2,5-di(3,4-dimethoxyphenylthio)benzene reacted with SCl_2 to yield a pentacycle comprising two overlapping thianthrene units [88ZN(B)599]. The use of SCl_2 in the presence of $SnCl_4$ allowed the synthesis of 2,3,7,8-bis(ethylenedioxy)thianthrene from di(3,4-ethylenedioxy)phenyl sulfide or the aromatic ether itself [88JCS(P1)2095].

2. From Aryl Thiols and Diaryl Sulfides

It is not surprising that in attempted $AlCl_3$ catalysis of the reaction between thiophenol and various lactones, considerable amounts of thianthrene were obtained from a side reaction (81JOC5163). A low yield of thianthrene itself was obtained by converting *o*-bromobenzene thiol into its copper derivative (66JOC4071), but a good yield of thianthrene-2,3,7,8-tetracarboxylic acid **83** was observed from a hot reaction between **84** with cuprous oxide in DMF (82MI5). The saturated *o*-chlorobenzene thiols, **85**



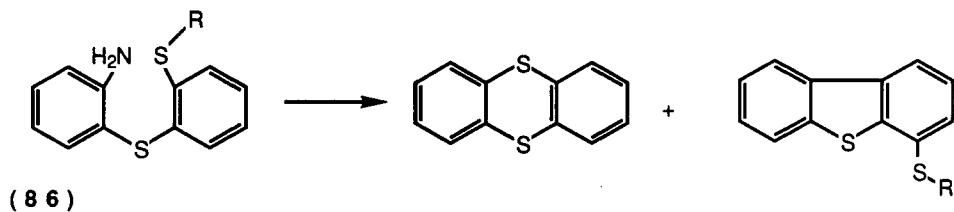
($\text{R} = \text{Cl}, \text{NO}_2$) were converted into the 2,7-disubstituted thianthrenes at room temperature and 130°C , respectively by $\text{Et}_3\text{N}/\text{HMPA}$ (83SC1181).

Octachlorothianthrene resulted from a 24 hr irradiation of pentachlorophenylsulfenyl chloride. However, after a 150 hr irradiation, octachlororodibenthien was produced; the intermediacy of the former in the production of the latter is clearly implied, but was not proved [65CI(L)302].

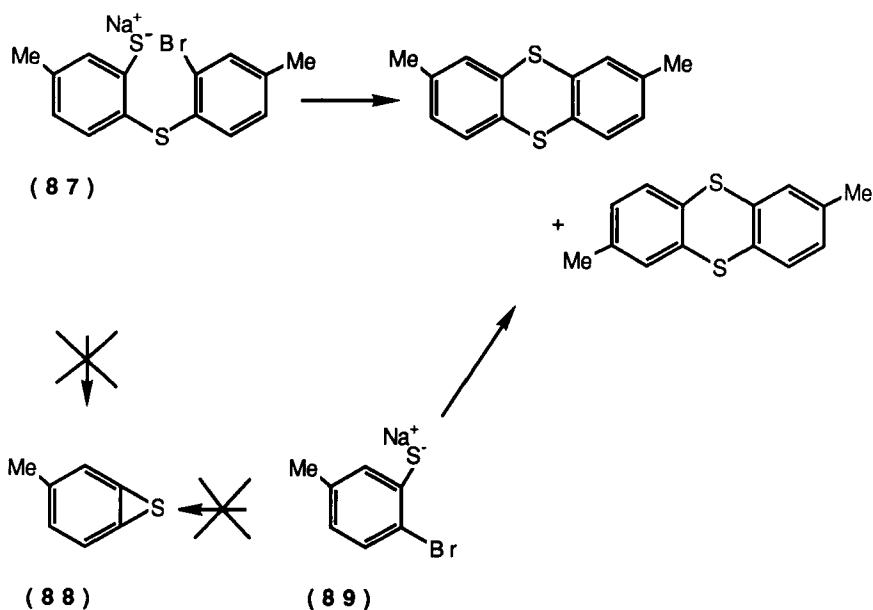
Thianthrene is not produced from diphenyl sulfide/ AlCl_3 until the temperature is greater than 70°C . Below that temperature, complex formation, presumably between sulfur and Lewis acid, is all that occurs (80MI9). A 68% yield (allowing for recovered starting material) of thianthrene was claimed from diphenyl sulfide/ AlCl_3 in dry air at 170°C (70IZV2752), while at 180 – 250°C , only polymer and benzene were obtained (86MI3). A 70% yield of thianthrene resulted from an $\text{AlCl}_3/130^\circ\text{C}$ treatment of poly(1,4-phenylenesulfide) (86MI3). Dechlorination took place when di(4-chlorophenyl) sulfide and 4-chlorophenyl sulfide were treated with $\text{S}/\text{AlCl}_3/100^\circ\text{C}$; the former gave mainly 2-chlorothianthrene, and the latter gave mainly thianthrene [68JCS(C)1230].

Aprotic diazotization of **86** ($\text{R} = \text{Me}$ or Ph) produced 55% of thianthrene and lesser amounts of 1-phenylthio- (or methylthio) dibenzothiophen (Scheme 14) together with deaminated products. Comparable yields of 2-methyl-, 2-methoxy-, 2,7-dichloro- and 2,8-dichlorothianthrenes were obtained using this synthetic route. It is suggested that ring closure involves an intramolecular homolytic substitution at sulfur with loss of the S -substituent as a radical [74JCS(P1)1272].

Heating the sodium salt **87** at 240°C gave both 2,7-di- and 2,8-dimethylthianthrenes, which was taken [77DIS(B)701] to indicate a Smiles rearrangement and negate the need to postulate (74CC900) an intermediate benzothiirene (**88**) in the formation of these two isomers by heating **89**.



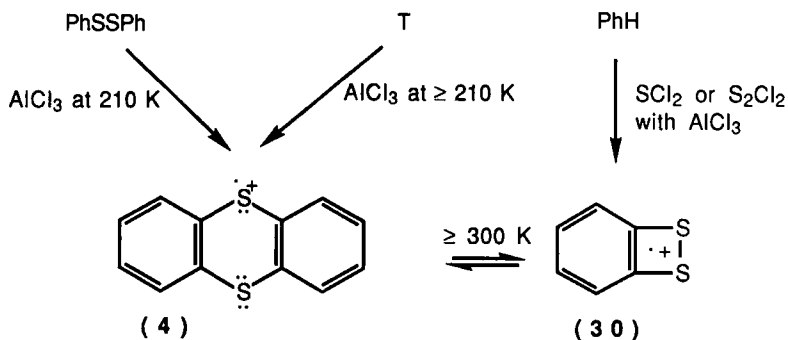
SCHEME 14



After (presumed) *S*-alkylation of diphenyl sulfide with Meerwein's reagent, heating the resultant material at 175°C gave a small quantity of thianthrene as a component of a complex product mixture (71JOC1513).

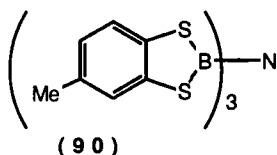
3. From Diaryl Disulfides

A detailed study of the interaction of diaryl sulfides with AlCl_3 (unsubstituted and *p*-chloro, methoxy, and fluoro) at -60°C showed the corresponding thianthrene radical ions(1+) to have been formed. Bis (4-nitrophenyl)disulfide produced thianthrene radical ion(1+) itself. The



SCHEME 15

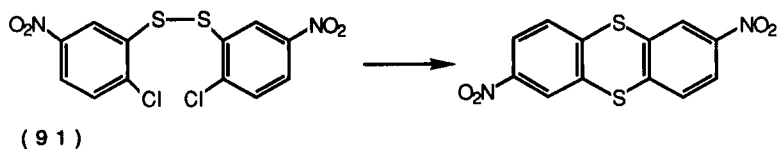
solution of thianthrene radical ions(1+), warmed to $\geq 300^\circ\text{K}$, gave a benzodithiete (30) in the unsubstituted case, which was detected by ESR spectroscopy. This same benzodithiete radical cation was formed directly from benzene with *either* SCl_2 or $\text{S}_2\text{Cl}_2/\text{AlCl}_3$ in CH_2Cl_2 . Aluminum chloride converts the amino-borane 90 immediately into the benzodithiete

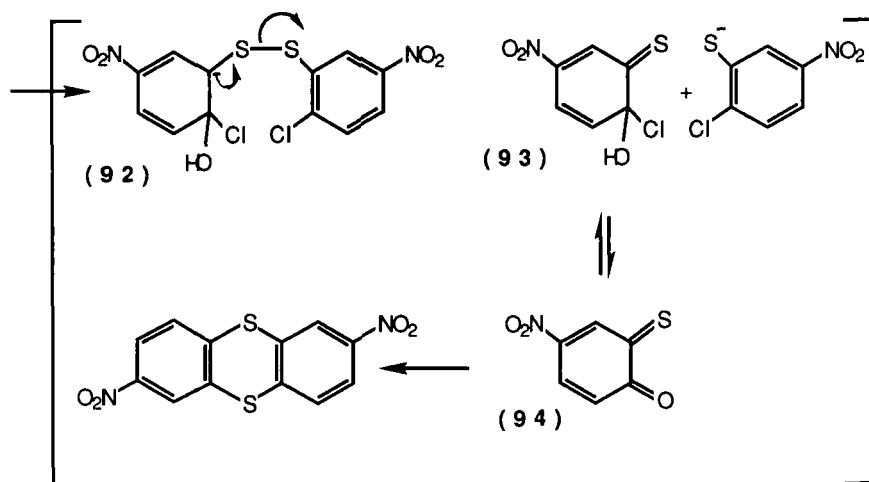


and hence to the thianthrene radical ion(1+) (82CB2548). Scheme 15 summarizes these findings.

2,7-Di-*tert*-butylthianthrene and 1,3,6,8-tetra-*tert*-butylthianthrene were obtained from the diaryl sulfides in moderate yields by reaction with *c.* H_2SO_4 in nitromethane (68CB2956). A modified diaryl disulfide approach was based on intramolecular free radical substitution: an *o*-phenoxy- (95% yield) or *o*-phenylthio-substituent (40% yield) being displaced as a radical (75G841).

Base treatment of 91 produced 79% 2,7-dinitrothianthrene; perhaps intermediates 92, 93, and 94 are involved (84ZOR202).



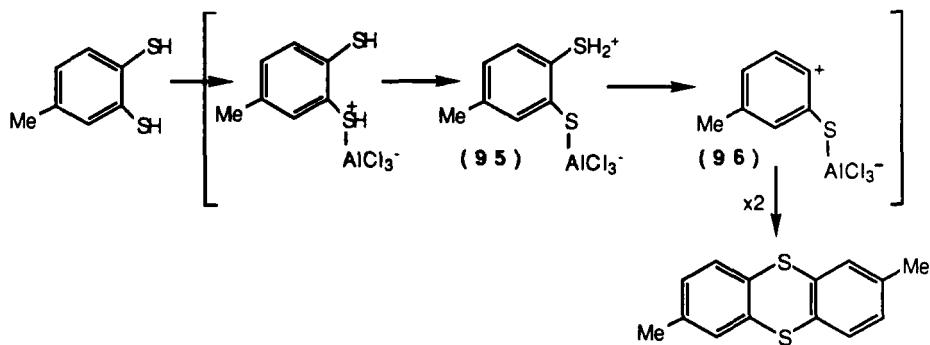


Phenylsulfenyl fluoride was detected by ^{19}F -NMR in the reaction mixture during the conversion of diphenyl disulfide into thianthrene using SF_4 (78MI1).

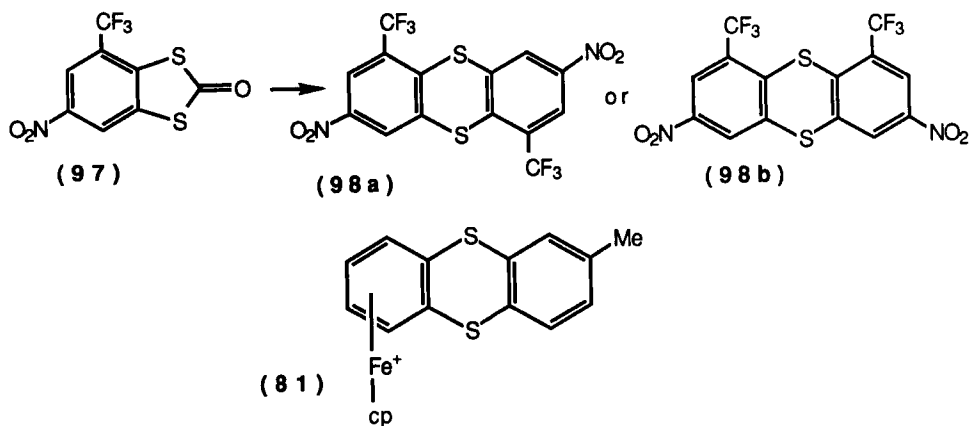
4. From *o*-Disulfur-Substituted Arenes

Aluminum chloride or gallium trichloride (82MI3) or trimethylaluminum (82MI2) convert 4-methylbenzene-1,2-dithiol into the radical cation of 2,7-dimethylthianthrene; the rather unlikely loss of hydrogen sulfide in a step, **95** \rightarrow **96**, was imputed (Scheme 16).

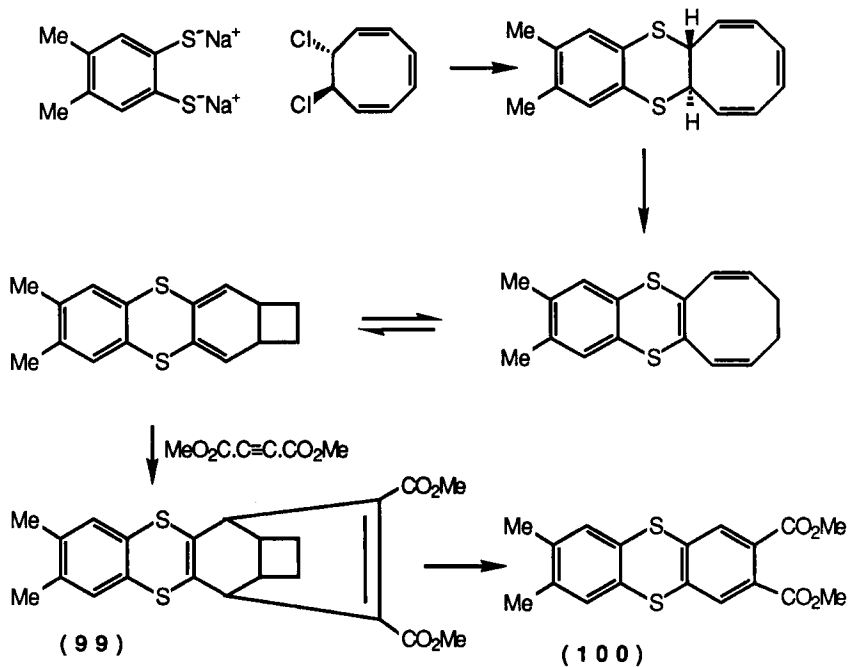
When the dithiophenolate is liberated from **97** with a mol equivalent of NaOH in Me_2SO , the thianthrene **98a** or **98b** resulted (80JOC4806).



SCHEME 16



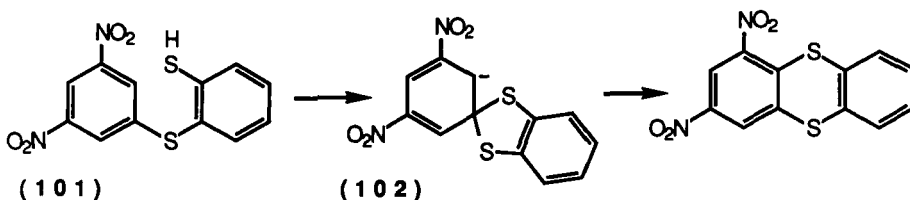
Direct formation of an organometallic complex **81** resulted when (η^6 -*o*-dichlorobenzene)(η^6 -cyclopentadienyl)iron(II) hexafluorophosphate was reacted with 4-methylbenzene-1,2-dithiol. The free 2-methylthianthrene could be released by heating the complex to 200–250°C (82JHC801). 4,5-



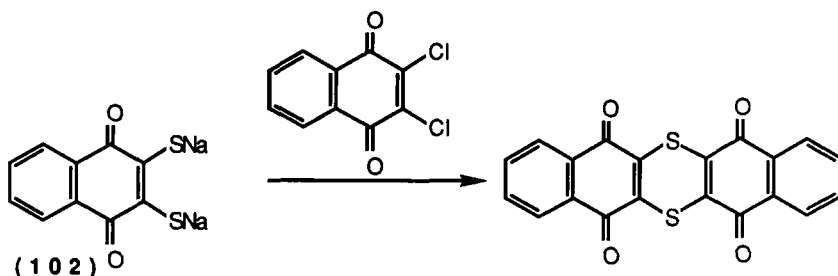
SCHEME 17

Dimethylbenzene-1,2-dithiol disodium salt reacted with *trans*-1,2-dichlorocycloocta-3,5,7-triene and then dimethyl acetylenedicarboxylate in a sequence (Scheme 17) that finally resulted in **99**, which on heating lost cyclobutene and gave the thianthrene diester **100** (78CC57).

The thiol-diarylsulfide **101** produced a Meisenheimer salt that underwent rearrangement and eventually resulted in the production of 1,3-dinitrothianthrene (75ZOR1440).

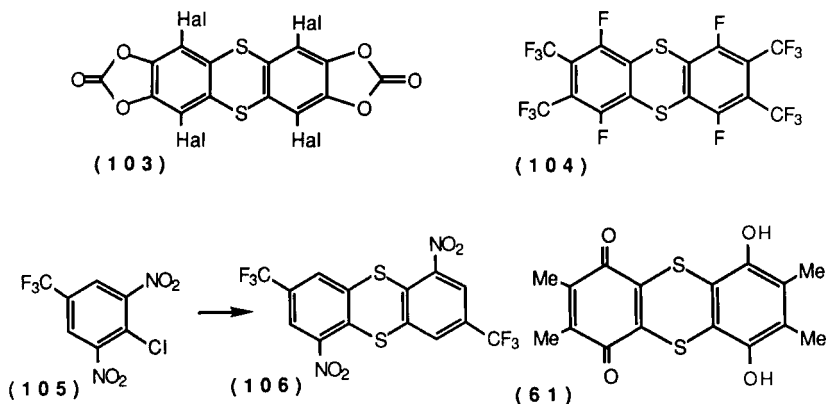


The ene-dithiolate unit in **102** was reacted with di- and tetrachloroquinones to produce polycyclic thianthrenes (88JHC901).



5. From *o*-Dihalogen-Substituted Arenes and Related Substances

1,2-Dichloro- or -dibromobenzenes are converted in good yields into thianthrene by reaction with H_2S at 550°C (76URP462468; 78ZOR2611). Apparently the comparably high temperature interactions of 1,2-dihalobenzenes with phenylthiol also lead to thianthrene (76ZOR1367). Lower temperatures suffice for converting 1,2-di-iodo-3,4,5,6-tetrafluorobenzene into octafluorothianthrene (230°C) (68JOM563) or tetrachloro (or -bromo) phthalic anhydride into **103** with sulfur (340°C) (74GEP2224834). A 60°C /thiourea reaction transformed 1,2,3,4-tetrafluoro-5,6-bistrifluoromethylbenzene into **104** (72T105). The highly activated **105** reacted with potassium ethyl xanthate at 85°C to give thianthrene **106** (77JOC2896), and Na_2S in hot ethanol was sufficient to convert 2,3-dichloro-5,6-dimethyl-*p*-benzoquinone into **61** (69CB1739).



$S_{RN}1$ processes have been shown to be relevant to the synthesis of simple thianthrenes which is done by irradiating the disodium salt of 4-methylbenzene-1,2-dithiol in the presence of 1,2-bromochlorobenzene (55%) or 1,2-di-iodobenzene (64%). More complex, fused thianthrenes result from 1-bromo-2-iodonaphthalene (24%, 2 isomeric products) and 2,3-dichloroquinoxaline (100%). These clearly hold considerable promise for the controlled construction of unsymmetrical thianthrenes (87JOC1089).

6. Synthesis from 2-Halobenzenesulfinic Acids

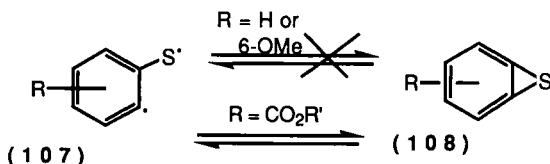
Early work (66HC1155) had already demonstrated the utility of an approach to thianthrenes in which a 2-chloro-5-nitrobenzenesulfinic acid is first reacted with an arylthiolate, and then ring closure is effected in an intramolecular sulfination, generating a thianthrene oxide that is reduced, often by simply leaving the acidic reaction mixture (23JCS156) or separately treating the product, still containing oxide, with HBr/AcOH (23JCS2786) (Section III,B,3,b). This process (shown generally in Scheme 11) has been further used to synthesize 2,8-dinitrothianthrene (80MI2) and 7-nitrothianthrene-1-carboxylic acid (71RC107).

C. SYNTHESIS FROM OTHER HETEROCYCLIC SYSTEMS

1. From 1,2,3-Benzothiadiazoles

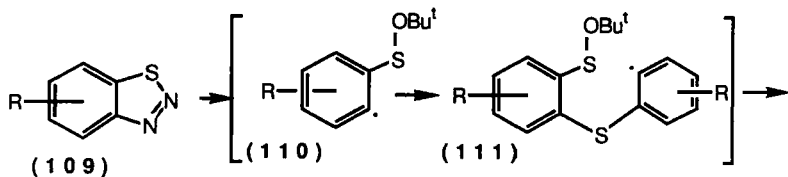
When a 1,2,3-benzothiadiazole is caused to lose nitrogen, thermally or photochemically, the resulting species can dimerize to produce a thianthrene, good yields being obtained in favorable cases. The parent hetero-

cycle reportedly gave only 7% thianthrene itself upon heating in digol at 240°C (75JHC605) [though better yields were later reported for this solvent (84CB107)] or neat at 240°C (77T449; 84CB107) and 42% in ethyl acetate at 220°C (77JOC575). The reaction intermediate is viewed (84CB107) as di-radical **107**; consequently thermolyses in arene solvents can lead to attack on the solvent by the intermediate and the formation of unsymmetrical thianthrenes (77JOC575). *o*-Thianthrene, debenzothiophen, diphenyl disulfide, and phenylthiol are usually byproducts in thianthrene syntheses from 1,2,3-benzothiadiazoles.



That 6-methoxy-1,2,3-benzothiadiazole (77JOC575) gave *only* 2,7-dimethoxythianthrene was interpreted as evidence against the collapse of diradical to benzothiirene **108** as had been earlier suggested (74CC900). This view was later confirmed (84CB107), at least for the parent heterocycle, by ¹³C-labeling of the aromatic ring. However, studies on 7-ester derivatives showed that this substituent presumably *did* allow closure, for both 2,7- and 2,8-dialkoxycarbonylthianthrenes were produced in the photochemical (84CB107) and thermal (77TL2643) decompositions. An 80% yield of thianthrene itself was realized photochemically (84CB107). Thermolysis neat at 240°C gave a better ratio of thianthrene to other products than in tetralin (207°C) or sulfolane (285°C) (84CB107).

Exposure of 1,2,3-benzothiadiazoles to free-radical reagents can also initiate nitrogen loss and subsequent formation of thianthrenes. Thus, **109** (R = 6-Cl, -MeO, -MeO₂C; 7-Me fails), when treated with di-*tert*-butylperoxide in refluxing benzene and via presumed intermediates **110** and **111**, gave the 2,7-disubstituted thianthrenes more cleanly than by thermolysis (81JOC4998). Exposure to phenyl radicals [74JCS(P1)1276] or to phenylnitrene (80CC715) or to diphenylcarbene [81JCS(P1)1544] also led to the formation of thianthrenes, but in complex product mixtures.

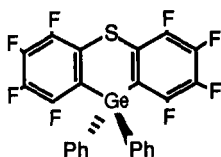


2. From 1,4,2-Benzodithiazine

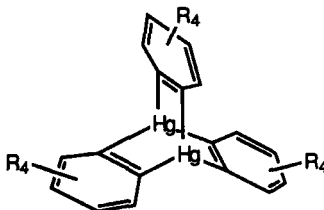
Generation of benzyne in the presence of 1,4,2-benzodithiazine gave a low yield of thianthrene among a complex product mixture (82CC612).

3. From Germanium, Mercury, and Tellurium Heterocycles

The octafluorodiphenylgermanium heterocycle **112** gave octafluorothianthrene upon heating with sulfur at 230°C (68JOM341). The tris-1,2-phenylene mercury heterocycles **113** (R = H, F, and Cl) produced the



(112)



(113)

corresponding thianthrenes with sulfur at 250°C (87JOM59). Phenothiatellurine was converted into thianthrene upon reaction with sulfur (70RRC1967).

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A 5% yield of thianthrene was obtained by generating benzyne in the presence of sulfur (87NKK1424).

V. Applications

2,7-Dimethylthianthrene is an ingredient in shampoos and soaps used to control scabies, pediculosis, seborrhea, and pruritis [71AX(B)1523; 81MIP1, 85JAP(K)59232198], and in admixture with ditoluene disulfide, it is used as a skin cosmetic [81JAP(K)55151507] for the removal of freckles (though why this should be seen to be desirable escapes this reviewer).

In the hope that thianthrene could be a probe for sulfonation enzymes, its metabolism in the rat was studied. It was found, however, that the major metabolic fate of the thianthrene was C-hydroxylation and not S-oxidation (79MI1). Thianthrene is hepatotoxic to rats of either sex (87MI5).

2,3,7,8-Tetrachlorothianthrene is useful as a co-catalyst with AlCl_3 [or SbCl_5 (78VSP4069263)] to encourage *p*-chlorination of toluene (77USP3989715; 80USP4190609). The time for co-catalyzed perhydrogenation of 1-methylnaphthalene was reduced by adding 0.2% thianthrene (67USP3324190). Thianthrene radical ion(1+) is said to be useful for the polymerization of cyclic ethers and cyclic acetals (82MIP1).

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